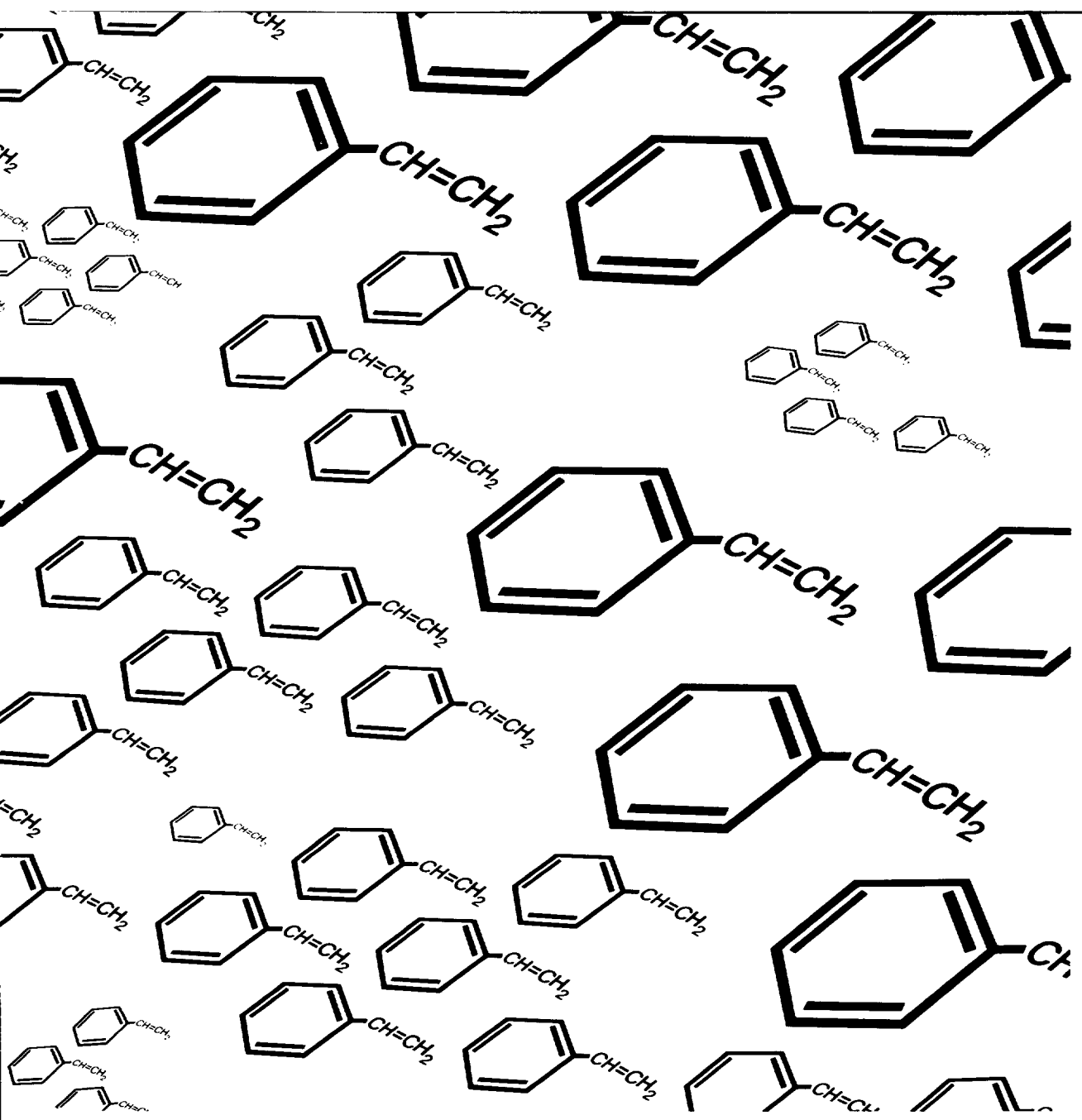

criteria for a recommended standard . . .

occupational exposure to styrene

NIOSH

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
CENTERS FOR DISEASE CONTROL
NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH

CRITERIA FOR A RECOMMENDED STANDARD....

OCCUPATIONAL EXPOSURE TO STYRENE

U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

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PREFACE

The Occupational Safety and Health Act of 1970 (Public Law 91-596) states that the purpose of Congress expressed in the Act is "to assure so far as possible every working man and woman in the Nation safe and healthful working conditions and to preserve our human resources...by," among other things, "providing medical criteria which will assure insofar as practicable that no employee will suffer diminished health, functional capacity, or life expectancy as a result of his work experience." Later in the Act, the National Institute for Occupational Safety and Health (NIOSH) is specifically authorized to "develop and establish recommended occupational safety and health standards" and to "conduct such research and experimental programs as....are necessary for the development of criteria for new and improved occupational safety and health standards."

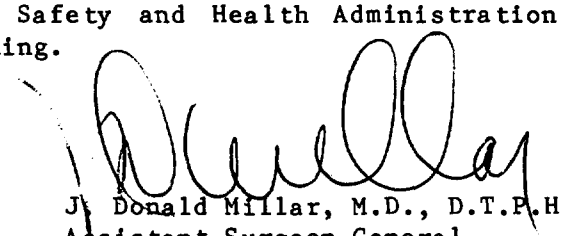
The Institute responds to these mandates by means of the Criteria Document. The essential and distinguishing feature of a Criteria Document is that it recommends a standard for promulgation by an appropriate regulatory body, usually the Occupational Safety and Health Administration or the Mine Safety and Health Administration of the U. S. Department of Labor.

The development of a Criteria Document entails a critical evaluation of all available scientific data pertinent to the subject, the writing of a draft Criteria Document, a systematic external review of the draft by acknowledged experts in the field, the incorporation of their relevant comments and suggestions, a review by the Office of the Director of NIOSH, the printing of a final version, and the delivery of the Criteria Document to the appropriate regulatory body. This process is lengthy and the typical Criteria Document is usually two to three years in the making.

Because they encompass thorough systematic reviews of available information, Criteria Documents generally prove to be of considerable interest and utility far beyond the regulatory process. Information contained in them is useful to both labor and management, and to official health agencies in reducing the hazards of work. Moreover, they have proven useful to voluntary agencies seeking to assist these efforts, and to academicians instructing students in principles of occupational safety and health. It is our intention that the information contained in these documents be disseminated as widely as possible among those with a need to know, in order to protect the health and safety of workers.

I am pleased to acknowledge the many contributions to this Criteria Document on styrene made by external consultants; representatives of the United Rubber Workers International Union and the Oil, Chemical, and Atomic Workers International Union; reviewers selected by The Society of Occupational and Environmental Health, the American Occupational Medical Association, the Society of the Plastics Industry, Inc., and the Chemical Manufacturers Association; representatives of other federal agencies; and, of course, the staff of the Institute (a list of consultants and agencies

receiving the draft Document for review, appears on pages vi-viii). However, responsibility for the conclusions reached and the recommendations made, belongs solely to the Institute. All comments by reviewers, whether or not incorporated into the final version, are being sent with the Criteria Document to the Occupational Safety and Health Administration (OSHA) for consideration in standard setting.



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I. RECOMMENDATIONS FOR A STYRENE STANDARD

The National Institute for Occupational Safety and Health (NIOSH) recommends that worker exposure to styrene in the workplace be controlled by compliance with the following sections. These recommendations are designed to protect the health and provide for the safety of workers for up to a 10-hour workshift, 40-hour workweek, over a working lifetime. Compliance with all sections of the recommended standard should prevent or greatly reduce the risk to exposed workers of adverse effects. NIOSH considers the recommended environmental limits for styrene to be upper boundaries of exposure. Thus, employers should make every effort to maintain exposure concentrations as low as possible. This recommended standard will be subject to review and revision as necessary.

Occupational injury and illness attributed to styrene results from inhalation of the vapor or from skin contact with the readily absorbed liquid. The NIOSH recommended standard is primarily based on reports of effects on the human nervous system, and on irritation of the eyes and respiratory system.

Central nervous system (CNS) effects have been observed among experimental subjects as well as workers exposed to styrene at time-weighted average (TWA) concentrations of about 100 parts per million (ppm). In addition, some investigators have reported observing these effects at concentrations less than 100 ppm, both experimentally and clinically. However, the experimental studies are of limited value in establishing a recommended exposure limit because of the small numbers of subjects studied. Similarly, the clinical studies are difficult to interpret because the exposures occurred over a wide range of concentrations, occasionally in excess of 100 ppm. The most frequently reported effects of exposures at about 100 ppm are subjective symptoms such as fatigue, dizziness, headache, nausea, poor memory, and drowsiness. These subjective symptoms of CNS depression have been substantiated experimentally in human subjects and in clinical studies of workers exposed to styrene who demonstrated slower reaction times and impaired balance; abnormal EEGs have also been noted.

It has been reported in a number of clinical studies that chromosome changes occurred with greater frequency in the lymphocytes of workers exposed to styrene at about 100 ppm than among workers not exposed to styrene. Other investigators have reported an increase in the rate of sister chromatid exchanges among styrene-exposed workers. However, the long-term significance of these effects is not clear and requires further elucidation.

Although the evidence is not strong, exposure to styrene has also been implicated with other adverse health effects such as peripheral neuropathy, abnormal pulmonary function, liver toxicity, teratogenicity, and

carcinogenicity. These health effects need further investigation, and would provide additional evidence for a reduction in the current occupational exposure standard if they were found to be styrene-related.

Although additional research is needed to clarify some of the reported effects, worker exposure to styrene should not exceed 50 ppm as a TWA concentration for up to a 10-hour workshift, 40-hour workweek. To prevent CNS depression and irritation of the eyes and respiratory tract, exposures should not exceed 100 ppm, determined as a ceiling concentration by a 15-minute sample.

The "action level" for styrene is defined as one-half the TWA concentration limit for styrene. Due to interday variability of environmental levels, a worker's single TWA exposure measurement over the workshift that is below the recommended standard does not necessarily indicate that exposures on other days would also be below the recommended standard. If a worker's TWA exposure during a workshift is at or above one-half the recommended standard, a sufficient probability exists that on other days exposures could exceed the recommended TWA standard. As such, the concept of an "action level" is needed to ensure adequate protection of the workers. Exposure to styrene below the "action level" will require adherence to all sections of the recommended standard except Sections 2(b), 8(a)(2), and the monitoring provisions of 8(b).

Section 1 - Environmental (Workplace Air)

(a) Concentration (Recommended Environmental Limits)

Exposure to styrene in the workplace shall be controlled so that workers are not exposed to styrene at concentrations greater than 50 parts per million (ppm), determined as a time-weighted average (TWA) exposure concentration for up to a 10-hour workshift, 40-hour workweek. A ceiling concentration of 100 ppm, as determined during any 15-minute sampling period, is also recommended.

(b) Sampling and Analysis

Workroom air samples shall be collected and analyzed as described in Appendix I, or by any other methods at least equivalent in accuracy, precision, and sensitivity.

Section 2 - Medical

The employer shall provide the following information to the physician performing or responsible for the medical surveillance program: the requirements of the applicable standard; an estimate of the worker's potential exposure to styrene, including any available workplace sampling results; a description of the worker's duties as they relate to the

workers's exposure; and a description of any protective equipment the worker may be required to use.

(a) Preplacement medical examinations shall include at least:

(1) Comprehensive medical and work histories with special emphasis on the nervous system, skin, respiratory tract, liver, and eyes.

(2) A physical examination giving special attention to the nervous system, skin, respiratory tract, liver, and eyes. Additional testing, such as clinical tests of liver function and enzymes, should be considered by the physician responsible for the examination.

(3) A judgment of the worker's ability to use positive and negative pressure respirators.

(b) Periodic medical examinations shall be made available at least annually to all workers occupationally exposed to styrene at airborne concentrations at or above the action level, or who have the potential for significant skin exposure (see paragraph (b)(3) of this section). These examinations shall include at least:

(1) An update of medical and work histories.

(2) A physical examination and tests as outlined in paragraph (a)(2) of this section.

(3) In those instances where there is a potential for elevated or widely varying styrene exposures through inhalation and/or skin absorption, measurement of urinary mandelic acid (a styrene metabolite) may serve as a useful adjunct for characterization of workplace styrene exposures (see Appendix II). If the measurement of a worker's urinary mandelic acid suggests possible overexposure to styrene, an effort should be made to ascertain the cause, such as failure of engineering controls, poor work practices, or nonoccupational exposures.

(c) Monitoring of urinary mandelic acid and a physical examination as outlined in paragraph (a)(2) of this section shall be made available to any worker exposed to unknown concentrations of styrene during a spill or emergency.

(d) Workers and potential workers having medical conditions, such as disorders of the nervous or respiratory systems, or a liver disease that could be directly or indirectly aggravated by exposure to styrene, shall be counseled on the possibility of increased risk of impairment to their health from working with styrene.

(e) Following completion of the examination, the physician shall give to the employer a written statement about whether the worker has any detected medical conditions which would place the worker at increased risk

of health impairment from exposure to styrene. The written statement shall include any recommended limitations upon the worker's exposure to styrene or upon the use of respirators. A copy of this written statement obtained by the employer shall not reveal specific findings or diagnoses and shall be provided to the worker.

(f) Pertinent medical records (i.e., the physician's written statement, the results of medical examinations and tests, medical complaints, etc.) for all workers subject to exposure to styrene in the workplace shall be retained for at least 30 years after termination of employment. Copies of environmental monitoring data applicable to a worker shall also be included in that worker's medical records. These records shall be made available to the designated medical representatives of the Secretary of Labor, the Secretary of Health and Human Services, the employer, and the worker or former worker.

(g) The relationship of styrene exposure to adverse reproductive effects has not been thoroughly investigated. Workers shall be made aware of the possibility of such adverse effects.

Section 3 - Labeling and Posting

All labels and warning signs shall be printed both in English and in the predominant language of non-English-reading workers. Workers unable to read the labels and posted signs shall be informed verbally regarding the hazardous areas of the plant or worksite and the instructions printed on labels and signs.

(a) Labeling

Containers of styrene used or stored in the workplace shall carry a permanently attached label that is readily visible. The label shall identify the presence of styrene and give information regarding its effects on human health. The information may be arranged as follows.

STYRENE

CAUTION!

HARMFUL IF INHALED OR IF ABSORBED THROUGH SKIN

IRRITATING TO SKIN, EYES, NOSE, THROAT, MOUTH, AND LUNGS

FLAMMABLE

In case of eye contact, immediately flush eyes with large amounts of water for 15 minutes.
If irritation persists, get medical attention.
Keep containers closed when not in use.
Use only with adequate ventilation.
Keep away from heat, sparks, and open flame.

(b) Posting

Readily visible signs containing information on the effects of styrene on human health and emergency measures shall be posted in work areas and at entrances to work areas or building enclosures where there is the likelihood of styrene concentrations above the action level or where the possibility of appreciable spills or skin contact with styrene exist. This information may be arranged as follows.

STYRENE

CAUTION!

HARMFUL IF INHALED OR IF ABSORBED THROUGH SKIN

IRRITATING TO SKIN, EYES, NOSE, THROAT, MOUTH, AND LUNGS

FLAMMABLE

Place cleaning rags and soiled clothing in fireproof containers.
Use chemical fire extinguisher.

(c) Respirators

If respirators are needed during the installation or implementation of required engineering controls, the following statement shall be added in large letters to the sign required in paragraph (b) of this section:

RESPIRATORY PROTECTION REQUIRED IN THIS AREA

(d) Emergency Situations

In any area where there is a likelihood of emergency situations arising, signs required by paragraph (b) of this section shall be supplemented with signs giving emergency and first-aid instructions and procedures, the location of first-aid supplies and emergency equipment, and the locations of emergency showers and eyewash fountains.

Section 4 - Protective Clothing and Equipment

Engineering controls and safe work practices shall be used to keep the concentration of airborne styrene at or below the limits specified in Section 1(a) and to minimize skin and eye contact. In addition, protective clothing and equipment shall be provided by the employer to the workers when necessary.

(a) Eye Protection

The employer shall provide safety glasses, chemical safety goggles, or face shields (20-cm minimum) with goggles and shall ensure that workers wear the protective equipment during any operation in which splashes of liquid styrene are likely to occur. Devices for eye and face protection shall be selected, used, and maintained in accordance with 29 CFR 1910.133 (U.S. Department of Labor, Occupational Safety and Health Administration, Occupational Safety and Health Standards, Eye and Face Protection).

(b) Skin Protection

(1) Workers at risk of skin contact with styrene shall be provided with protective clothing such as gloves, boots, overshoes, and bib-type aprons (at least knee-length). The clothing shall be both impervious and resistant to styrene. Materials made of polyvinyl alcohol or polyethylene afford good protection.

(2) Clothing contaminated with styrene shall be cleaned before reuse. Anyone who handles contaminated clothing or is responsible for its cleaning shall be informed of the hazards of styrene and the proper precautions for its safe handling and use.

(3) The employer shall ensure that all personal protective clothing and equipment is inspected regularly and maintained in a clean and satisfactory working condition.

(c) Respiratory Protection

(1) The use of a respirator to achieve compliance with the recommended exposure limits is permitted only during the time necessary to install and test required engineering controls, for nonroutine operations such as maintenance or repair activities causing brief exposures at concentrations in excess of the recommended environmental limits, during work in confined spaces, or during emergencies when concentrations of airborne styrene may exceed the recommended environmental limit.

(2) Respirators shall be provided in accordance with Table I-1 by the employer when such equipment is necessary to protect the health of the worker. The worker shall use the provided respiratory protection in accordance with instructions and training received.

(3) The respiratory protective devices provided in conformance with Table I-1 shall comply with the standards jointly approved by NIOSH and the Mine Safety and Health Administration (MSHA) as specified under the provisions of the U.S. Department of the Interior, Bureau of Mines (Respiratory Protective Devices and Tests for Permissibility, 30 CFR Part 11).

(4) The employer shall ensure that respirators are properly fitted and that workers are instructed at least annually in the proper use and testing for leakage of respirators assigned to them.

(5) The employer shall be responsible for the establishment and maintenance of a respiratory protection program meeting or exceeding the requirements established by the Occupational Safety and Health Administration (Respiratory Protection, 29 CFR 1910.134) as summarized below:

(A) Written standard operating procedures governing use of respirators shall be established.

(B) The worker shall be instructed and trained in the proper use of respirators and their limitations.

(C) Where practicable, the respirators should be assigned to individual workers for their exclusive use.

(D) Respirators shall be regularly cleaned and disinfected.

(E) Respirators shall be stored in a convenient, clean, and sanitary location.

(F) Respirators used routinely shall be inspected during cleaning. Worn or deteriorated parts shall be replaced. Respirators for emergency use such as self-contained devices shall be thoroughly inspected at least once a month and after each use.

(G) Workers should not be assigned to tasks requiring use of respirators unless it has been determined that they are physically able to perform the work and use the equipment. The respirator user's medical status should be reviewed periodically (for instance, annually) as recommended by the physician responsible for the physical examination.

(H) Appropriate surveillance of work area conditions and degree of worker exposure or stress shall be maintained.

(I) There shall be regular inspection and evaluation by the employer to determine the continued effectiveness of the program.

Section 5 - Informing Workers of the Hazards of Styrene

(a) All new and current workers in areas where airborne exposures to styrene are at or above the action level, or who have the potential for significant skin exposure, shall be kept informed of the hazards, relevant prenarcotic symptoms, effects of overexposure, and proper conditions and precautions for the safe use and handling of styrene.

TABLE I-1

RESPIRATOR SELECTION GUIDE
FOR PROTECTION AGAINST STYRENE

Vapor Concentration	Respirator Type Approved Under Provisions of 30 CFR 11*
400 ppm or less	Any chemical cartridge respirator with organic vapor cartridge(s).**
	Any supplied-air respirator.**
	Any self-contained breathing apparatus.**
1000 ppm or less	A chemical cartridge respirator with a full facepiece and organic vapor cartridge(s).
5000 ppm or less	A gas mask with a chin-style or front- or back-mounted organic vapor canister.
	Any supplied-air respirator with a full facepiece, helmet, or hood.
	Any self-contained breathing apparatus with a full facepiece.
Greater than 5000 ppm or during entry and escape from unknown concentrations.	Self-contained breathing apparatus with a full facepiece operated in pressure-demand or other positive pressure mode.
	A combination respirator which includes a Type C supplied-air respirator with a full facepiece operated in pressure-demand or other positive pressure or continuous-flow mode and an auxiliary self-contained breathing apparatus operated in pressure-demand or other positive pressure mode.
Fire Fighting	Self-contained breathing apparatus with a full facepiece operated in pressure-demand or other positive pressure mode.
Escape	Any gas mask providing protection against organic vapors.
	Any escape self-contained breathing apparatus.

*Only NIOSH-approved or MSHA-approved equipment should be used.
**If eye irritation occurs, full-facepiece respiratory protective equipment should be used.

(b) The employer shall institute a continuing education program, conducted by persons qualified by experience or training in occupational safety and health, to ensure that all workers exposed to styrene above the action level have current knowledge of styrene hazards, proper maintenance, cleanup methods, and proper use of protective clothing and equipment, including respirators. The instructional program shall include oral and written descriptions of the environmental and medical surveillance programs and of the advantages to the worker of participating in these surveillance programs. The employer shall maintain a written plan of these training and surveillance programs.

(c) Workers shall also be instructed on their responsibilities for following proper work practices and sanitation procedures to help protect the health and provide for the safety of themselves and their fellow workers.

(d) All new and current workers in areas where exposure to styrene may reasonably be expected to occur during spills or emergencies shall be trained in proper emergency and/or evacuation procedures.

(e) Required information shall be recorded on the "Material Safety Data Sheet" shown in Appendix III, or on a similar form specified by the Occupational Safety and Health Administration (OSHA) describing the relevant toxic, physical, and chemical properties of styrene and of mixtures of styrene that are used or otherwise handled in the workplace. This information shall be kept on file and shall be readily available to workers for examination and copying.

Section 6 - Work Practices

(a) Handling and General Work Practices

(1) Operating instructions for all equipment shall be developed and posted where styrene is handled or used.

(2) Transportation and use of styrene shall comply with all applicable local, State, and Federal regulations.

(3) Styrene shall be stored in tightly closed containers in well-ventilated areas.

(4) Containers shall be moved only with the proper equipment and shall be secured to prevent loss of control or dropping during transport.

(5) Storage facilities shall be designed to contain spills completely within surrounding dikes and to prevent contamination of workroom air.

(6) Ventilation switches and emergency respiratory equipment shall be located outside storage areas in readily accessible locations that will remain only minimally contaminated with styrene in an emergency.

(7) Process valves and pumps shall be readily accessible and shall not be located in pits or congested areas.

(8) Styrene containers and systems shall be handled and opened with care. Approved protective clothing and equipment as specified in Section 4 shall be worn by workers who open, connect, and disconnect styrene containers and systems. Adequate ventilation shall be provided to minimize exposures of such workers to airborne styrene.

(9) Styrene storage equipment and systems shall be inspected daily for signs of leakage. All equipment, including valves, fittings, and connections, shall be checked for leaks immediately after styrene is introduced therein.

(10) When a leak is found, it shall be repaired promptly. Work shall resume normally only after necessary repair or replacement has been completed, and the area has been well ventilated.

(b) Engineering Controls

(1) Engineering controls shall be used when needed to maintain exposure to airborne styrene within the limits prescribed in Section 1(a). Complete containment of the vapor is the recommended method for control of styrene exposure. Local exhaust ventilation may also be effective when used alone or in combination with process enclosure. When a local exhaust ventilation system is used, it shall be designed and operated so as to prevent accumulation or recirculation of airborne styrene into the workplace environment and to effectively maintain safe levels of styrene in the breathing zones of workers. Exhaust ventilation systems discharging to outside air shall conform with applicable local, State, and Federal air pollution regulations and shall not constitute a hazard to workers or to the general population. Before maintenance work on control equipment begins, the generation of airborne styrene shall be eliminated to the extent feasible.

Enclosures, exhaust hoods, and ductwork shall be kept in good repair so that designed airflows are maintained. Measurements such as capture velocity, duct velocity, or static pressure shall be made at least semiannually, and preferably monthly, to demonstrate the effectiveness of the mechanical ventilation system. The use of continuous airflow indicators, such as water or oil manometers marked to indicate acceptable airflow, is recommended. A log shall be kept showing design airflow and the results of all airflow measurements. Measurements of the effectiveness of the system to control exposures shall also be made as soon as possible after any change in production, process, or control which may result in any increase in airborne concentrations of styrene.

(2) Forced-draft ventilation systems shall be equipped with remote manual controls and should be designed to shut off automatically in the event of a fire in the styrene work area.

(c) Confined or Enclosed Spaces

(1) Entry into confined or enclosed spaces, such as tanks, pits, tank cars, and process vessels, where there is limited egress, shall be controlled by a permit system. Permits shall be signed by an authorized employer representative and shall certify that preparation of the confined space, precautionary measures, and personal protective equipment are adequate and that precautions have been taken to ensure that prescribed procedures will be followed.

(2) Confined spaces that have contained styrene shall be thoroughly ventilated, inspected, and tested for oxygen deficiency and for the presence of styrene and any other known or suspected contaminants. Every effort shall be made to prevent inadvertent release of hazardous amounts of styrene into confined spaces in which work is in progress. Styrene supply lines shall be disconnected or blocked off before and while such work is in progress.

(3) No worker shall enter any confined space that does not have an entryway large enough to admit a worker wearing safety harness, lifeline, and appropriate respiratory equipment as specified in Section 4(c).

(4) Confined spaces shall be ventilated while work is in progress to keep the concentration of styrene at or below the recommended limits, to keep the concentration of other contaminants below dangerous levels, and to prevent oxygen deficiency.

(5) If the concentration of styrene in the confined space exceeds the recommended environmental limit, respiratory protective equipment is required for entry.

(6) Anyone entering a confined space shall be kept under observation from the outside by another properly trained and protected worker. An additional supplied-air or self-contained breathing apparatus with safety harness and lifeline shall be located outside the confined space for emergency use. The person entering the confined space shall maintain continuous communication with the standby worker.

(d) Emergency Procedures

Emergency plans and procedures shall be developed for all work areas where there is a potential for exposure to styrene. They shall include those procedures specified below as well as any others considered appropriate for a specific operation or process. Workers shall be instructed in the effective implementation of these plans and procedures.

(1) If styrene leaks or spills, the following steps shall be taken:

(A) All nonessential personnel shall be evacuated from the leak or spill area.

(B) The area where the leak or spill occurs shall be adequately ventilated to prevent the accumulation of vapor.

(C) The styrene shall be collected for reclamation or be absorbed on vermiculite, dry sand, earth, or similar nonreactive material and be disposed of properly.

(2) Only personnel trained in the emergency procedures and protected against the attendant hazards shall clean up spills, control and repair leaks, and fight fires in areas where styrene is present.

(3) Personnel entering the spill or leak area shall be furnished with appropriate personal protective clothing and equipment. Other personnel shall be prohibited from entering the area.

(4) Safety showers, eyewash fountains, and washroom facilities shall be provided, maintained in working condition, and located so as to be readily accessible to workers in all areas where skin or eye contact with styrene is likely. If styrene is splashed or spilled on a worker, contaminated clothing shall be removed promptly and the skin washed thoroughly with soap and water. Eyes splashed by styrene shall be irrigated immediately with a copious flow of water for 15 minutes. If irritation persists, get medical attention.

(e) Storage

Styrene shall be stored in well-ventilated areas and kept away from ignition sources such as heat or sparks and from oxidizing agents, catalysts, and strong acids. If styrene is stored more than 30 days at 32°C (about 90°F) or above, the inhibitor concentration shall be checked periodically. Large styrene storage containers should be installed with a temperature alarm system to signal interior temperature increases that may result in runaway polymerization, a special concern in hot climates. The rate of polymer formation in storage tanks can be reduced by cooling the tank by means of a water spray, refrigeration, insulation, or reflective painting. In a laboratory, samples of styrene may be stored in refrigerators or cold boxes.

Section 7 - Sanitation

(a) The preparation, storage, dispensing (including vending machines), or consumption of food shall be prohibited in areas where styrene is manufactured, formulated, processed, stored, or otherwise used.

(b) Smoking shall be prohibited in areas where styrene is manufactured, formulated, processed, stored, or otherwise used.

(c) Workers who handle styrene or equipment contaminated with styrene shall be instructed to wash their hands thoroughly with soap or mild detergent and water before eating, smoking, or using toilet facilities.

(d) Facilities such as double lockers should be provided for workers so soiled clothing can be stored separately from clean clothing.

Section 8 - Exposure Monitoring and Recordkeeping Requirements

(a) Exposure Monitoring

(1) The employer shall conduct an industrial hygiene survey to determine whether exposures to airborne concentrations of styrene are in excess of the action level (i.e., 25 ppm determined as a TWA over the workshift). The employer shall keep records of these surveys. If the employer concludes that exposures are below the action level, the records must show the basis for this conclusion. Surveys shall be repeated at least annually and within 30 days of any process change likely to result in an increased concentration of airborne styrene.

(2) If there is exposure to styrene at or above the action level, a program of personal monitoring shall be instituted to identify and measure, or to permit calculation of, the exposure of each worker occupationally exposed to airborne styrene. Source and area monitoring may be a useful supplement to personal monitoring. In all personal monitoring, samples representative of the TWA and ceiling exposures to airborne styrene shall be collected in the breathing zone of the worker. Procedures for sampling and analysis shall be in accordance with Section 1(b). For each determination of an occupational exposure concentration, a sufficient number of samples shall be collected to characterize each worker's exposure during each workshift. While all workers do not have to be monitored, sufficient samples should be collected to characterize the exposure of all workers. Variations in work and production schedules, as well as worker locations and job functions, shall be considered in decisions on sampling locations, times, and frequencies.

If a worker is found to be exposed to styrene at or above the action level but below the recommended environmental limits, the exposure of that worker shall be monitored at least once every 6 months or as otherwise indicated by a professional industrial hygienist. If a worker is found to be exposed to styrene in excess of the recommended environmental limits, controls shall be initiated, the worker shall be notified of the exposure and of the control measures being implemented, and the exposure of that worker shall be evaluated at least once a week. Such monitoring shall continue until two consecutive determinations, at least 1 week apart, indicate that the worker's exposure no longer exceeds the recommended limits. At that point, semiannual monitoring shall then be resumed.

(b) Recordkeeping

Records of the monitoring used to characterize the environmental exposures for each worker shall be retained for at least 30 years after the individual's employment has ended. These records shall include the name of the worker being monitored; Social Security number; duties performed and job locations within the worksite; dates and times of measurements; sampling and analytical methods used; number, duration, and results of samples taken; and the type of personal protection used, if any. Workers shall be able to obtain information on their own environmental exposures. Workplace environmental monitoring records shall be made available to designated representatives of the Secretary of Labor, the Secretary of Health and Human Services, and the worker or former worker.

Pertinent medical records (i.e., results of medical examination results, the physician's written opinion, medical complaints, medical and work histories, etc.) for all workers subject to exposure to styrene in the workplace shall be retained by the employer for at least 30 years after termination of employment. Copies of environmental monitoring data applicable to a worker shall be included in that worker's medical records. These medical records shall be made available to the designated medical representatives of the Secretary of Labor, the Secretary of Health and Human Services, the employer, and the worker or former worker.

II. INTRODUCTION

This report presents the criteria and recommended standards that have been prepared to meet the need for preventing impairment of health arising from exposure to styrene. The criteria document is developed by the Secretary of Health and Human Services, in response to Section 20(a)(3) of the Occupational Safety and Health Act of 1970, to "develop criteria dealing with toxic materials and harmful physical agents and substances which will describe...exposure levels at which no worker will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience."

NIOSH has formalized a system for the development of criteria on which standards could be established to protect the health and provide for the safety of workers from exposure to hazardous chemical and physical agents. The criteria and recommended standard are intended to enable management and labor to develop better engineering controls and more healthful work practices, and to comply with the recommended environmental limits should not be the final goal.

These criteria for a recommended standard for styrene are part of a continuing series of recommendations developed by NIOSH. The proposed standard applies only to workplace exposure arising from the processing, manufacturing, handling, and use of styrene. The standard is not designed for the population-at-large, and any extrapolation beyond the occupational environment is not warranted. It is intended to: (1) provide protection against the development of systemic effects and local effects on the skin and eyes of workers, and (2) be measurable by techniques that are valid, reproducible, and available to industry and government agencies.

Styrene is used extensively in the manufacture of plastics and rubber. The principal acute hazards from worker exposure to styrene are central nervous system (CNS) depression and irritation of the skin, eyes, and upper respiratory tract. The possibility of styrene-related adverse health effects such as damage to the central and peripheral nervous systems, birth defects, chromosomal aberrations, sister chromatid exchanges, unscheduled DNA synthesis, impaired pulmonary function, liver injury, and carcinogenicity has also been suggested. Further study of these latter effects will help to elucidate their etiology.

III. SCOPE OF THE DOCUMENT

This document assesses the hazards of occupational exposure to styrene, a commercially important compound. This chapter gives information on the physical and chemical properties of styrene, its production methods and uses, and the extent of worker exposure. Chapter IV discusses and summarizes the effects of styrene exposure on humans and animals. Subsequent chapters describe environmental sampling and analytical methods for styrene, biological monitoring techniques, existing occupational health standards, and a correlation of exposure and effect. In addition, methods for worker protection are discussed and include suggested work practices, engineering controls, personal protective clothing and equipment, and monitoring and recordkeeping.

Most of the clinical studies cited in Chapter IV. Effects of Exposure are based on the evaluation of workers in the reinforced plastics industry, along with a number of studies of workers who produce styrene and polystyrene. Since the formulation of styrene-butadiene rubber (SBR) involves numerous substances besides styrene and butadiene, and also since many other substances are emitted during vulcanization and curing, the likelihood of any effects being due to styrene alone are quite small, although styrene could be a contributing factor. For example, among workers who produce SBR, adrenocortical insufficiency [1], enlarged liver and spleen [2], inflammation of the gall bladder [2,3], and degeneration of the capillaries [4], have been reported. These effects are different from those reported to have occurred among workers in other occupational settings where styrene is made or used. A detailed discussion of the SBR industry is beyond the scope of this document.

Physical and Chemical Properties

Styrene, also known as vinylbenzene or phenylethylene, is an aromatic organic compound with the chemical formula $C_6H_5CH=CH_2$. Styrene is a volatile liquid with a low vapor pressure [5]. The odor threshold is below 1 ppm [6,7,8]. Identifiers for styrene include the Chemical Abstracts Service Registry No. 100-42-5 and the Registry of Toxic Effects of Chemical Substances No. WL3675000. Standard specifications for styrene have been issued by the American Society for Testing and Materials [9]. Styrene is soluble in many organic solvents, but only slightly soluble in water [10,11]. Other information about styrene, including some of its chemical and physical properties is given in Table III-1.

TABLE III-1

STYRENE PROPERTIES

Synonyms	Cinnamene, cinnamenol, cinnamol, ethenylbenzene, monostyrene, phenethylene, phenylethene, phenylethylene, stirolo (Italian), styreen (Dutch), styren (Czech), styrol(German), styrole, styrolene, styron, styropol, styropor, vinylbenzen (Czech), vinylbenzene, vinylbenzol
Molecular formula	$C_6H_5CH=CH_2$
Formula weight	104.16
Boiling point (760 mm Hg)	145.2°C (293.4°F)
Freezing point	-30.6°C (-23.1°F)
Density	0.9018 g/cu cm (25°C)
Solubility	Soluble in ethyl ether, benzene, methanol, toluene, ethanol, acetone, n-heptane, carbon tetrachloride, carbon disulfide; slightly soluble in water (about 25 mg/100 g water at 25°C)
Flammable (explosive) limits	1.1-6.1% by volume in air
Flashpoint	34.4°C (94°F) Tag closed cup 36.7°C (98°F) Tag open cup
Autoignition temperature	490°C (914°F)
Vapor Pressure	Temperature

°F	°C	mm Hg	kPa
50	10	2.34	0.31
68	20	4.50	0.60
77	25	6.45	0.86
86	30	8.21	1.09
104	40	14.30	1.91

Concentration in saturated air	8,500 ppm (25°C)
Conversion factors (25°C, 760 mm Hg)	1 ppm = 4.26 mg/cu m 1 mg/cu m = 0.235 ppm

Adapted from references [5,10,12,13,14,15]

Discovery of Styrene, Production Methods, and Uses

Styrene was isolated and described in 1831 by Bonastre who distilled a fragrant natural balsamic resin called liquid amber [16]; the reaction forming styrene was later shown to be the decarboxylation of cinnamic acid, a constituent of the natural resin [17]. Mention of a similar investigation by Neumann was made in 1795 by Nicholson [18]. A procedure for the synthesis of styrene was published in 1866 by Berthelot et al. [19], in which benzene and ethylene mixtures were passed through a heated porcelain tube.

Although styrene was known for many years to polymerize, the first successful production of high purity styrene was begun in 1925 by I.G. Farbenindustrie of Germany [20]. The first successful production of styrene in the United States (U.S.) was begun in 1930 by the Dow Chemical Company [17]. Today, most styrene continues to be produced by the catalytic dehydrogenation of ethylbenzene [21,22,23]. Recently, styrene has also been produced as a coproduct with propylene oxide. In this latter process, ethylbenzene is first oxidized to its peroxide and is then reacted with propylene to yield propylene oxide and alpha-methylphenyl carbinol; the carbinol is dehydrated to styrene [21,22,23]. Almost all of the ethylbenzene used in styrene production in the U.S. is obtained by on-site alkylation of benzene with ethylene [23]. A small amount (10-15 ppm) of p-tert-butylcatechol is added to the styrene monomer to prevent spontaneous polymerization [21].

The U.S. production of styrene grew from 2.4 million pounds in 1940 to 1,745 million pounds in 1960, to a peak of 7,473 million pounds in 1979 [23]. U.S. styrene production was 6,612 million pounds in 1981 [24]; in 1984, 62% is expected to be consumed in polystyrene production, 22% in copolymers such as styrene-acrylonitrile (SAN) and acrylonitrile-butadiene-styrene (ABS), 7% in styrene-butadiene rubber (SBR), 7% in unsaturated polyester resins, and 2% in miscellaneous uses [23]. Many consumer products are made from styrene-containing compounds including packaging and insulation from polystyrene, pipes and automotive components such as instrument panels and consoles from ABS, drinking tumblers and battery cases from SAN, carpet backcoatings from styrene-butadiene latexes, passenger car tires and industrial hoses from SBR, and boats and open storage tanks from unsaturated polyester resins. Some other end-uses of styrene are shown in Table XIII-1.

Worker Exposure

The number of workers in the U.S. potentially exposed to styrene is difficult to estimate. Currently, there are 13 facilities producing styrene monomer [23] which is mainly used as a constituent in a variety of different plastic and rubber items. Polystyrene is made at over 40 locations; other styrene-containing polymer resins such as ABS and SAN are also produced at about 40 locations with some facilities producing both types of resins [25,26,27]. About 20 facilities produce SBR and SBR latexes with 66% utilized in the tire and tire products industry [26,28]. Many plants are involved with the fabrication of reinforced plastics/composites, including hundreds of boat producers [26,29]. There are also hundreds of plastic fabrication facilities where polystyrene, ABS, SAN, etc., are custom molded, extruded, formed, or cast into thousands of finished products [26]. In these operations, styrene exposure is due to the unreacted residual monomer or the thermal degradation of the plastics. In addition, exposures to styrene may occur during the use of miscellaneous products containing styrene such as floor waxes and polishes, paints, adhesives, putty, metal cleaners, autobody fillers, and varnishes. NIOSH estimates that at least 30,000 workers in 1,000 plants are potentially exposed in the U.S. on a

full-time basis to styrene [30]. It is also estimated that compounds containing styrene are utilized in over 20,000 facilities with more than 300,000 workers potentially exposed [30]. In most of these latter facilities, the potentially exposed workers may not work directly with styrene or may only periodically come in contact with it. Tables XIII-2 and XIII-3 summarize styrene exposure levels found during industrial hygiene surveys in various industries.

In the past, workers involved in the production of styrene and polystyrene may have been significantly exposed to styrene and other toxic chemicals such as benzene and ethylbenzene [31]. The current use of closed systems in styrene monomer and copolymer resin production (i.e., polystyrene, ABS, SAN, SBR, etc.) limits exposures (for the most part) to spills, sample collections, the cleaning of vessels, and fugitive emissions from valves, pump seals, etc. [32,33]; full-shift TWA styrene exposures are generally less than 10 ppm. Usually, styrene exposures are also less than 10 ppm during the fabrication (i.e., molding, extruding, casting, etc.) of items from polystyrene or styrene copolymers which contain low residual levels of styrene monomer. The most substantial exposures to styrene occur when it is used as a solvent-reactant for unsaturated polyester products that have been reinforced with fibrous glass. For these reinforced plastic items such as boats, open storage tanks, wall panels, tub and shower units, and truck camper tops, The Society of the Plastics Industry, Inc. has given the formal designation of "reinforced plastics/composites" (RP/C) [34]. The very nature of many of these operations subjects workers to intimate contact with materials used in the process; workers may be exposed to high concentrations of styrene vapor and have skin contact with liquid styrene or resin. Average styrene exposures in RP/C plants can range from 40-100 ppm with individual TWA exposures often found as high as 150-300 ppm (see Table XIII-3). Short-term exposures (i.e., 5-15 minutes) of styrene in the 1,000-1,500 ppm range have also been reported in some RP/C plants [35,36].

In the fabrication of RP/C, after the surface of the mold is treated with a release agent (usually a wax) and the initial layer of resin (gel coat) is applied, hand lay-up or spray-up is done which consists of putting a layer of chopped fibers or woven mats of fibrous glass in place and then applying resin. Following disposition of fiber reinforcement and resin, it is necessary to roll-out or squeegee-out by hand the structure to saturate the fibrous glass with resin and to remove entrapped air. Other layers of glass fiber and resin are added and rolled out until the desired thickness is obtained. The styrene content in the resin is approximately 40 percent by weight [37,38]. High exposure levels of styrene (especially in building large items such as boats) occur during the manual spray-up or lay-up operations, since about 10 percent of the styrene evaporates into the workplace air as the resin cures [37,38]; the remainder of the styrene is consumed in the chemical reaction with the unsaturated polyester. The amount of styrene evolved is dependent on the surface area being fabricated, thickness of the laminate, ratio of resin to reinforcement, workshop temperature, and duration of each step in the process [39].

Workers exposed to styrene are usually also exposed to other chemicals as well. These potential exposures are to substances utilized as raw materials, solvents, catalysts, accelerators, or inhibitors; exposures are also possible to chemical intermediates, thermal degradation products, and resin-curing emissions. Table XIII-4 lists other substances that have been found (usually at low levels) in processes utilizing styrene or styrene-derivatives.

The Standard Industrial Classifications (SICs) of some of the industries with potential exposures to styrene are listed in Table XIII-5. In addition to occupational exposure to styrene, exposure may occur from styrene in community air [40,41,42], drinking water [43,44,45], fermented grains [46], food [47,48], toys [49], building panels, and floor coverings [50], and in the domestic usage of certain floor polishes, metal cleaners, or adhesives containing styrene.

IV. EFFECTS OF EXPOSURE

EFFECTS ON HUMANS

Historical Reports

As mentioned in the Scope of the Document, the first published reference to styrene was by Bonastre in 1831 who wrote: "Its odor is sharp, penetrating....Its taste is bitter, burning and caustic; an unpleasant sensation remains after tasting [16]." In a literature review published in the United States in 1940, Von Oettingen [51] reported that the toxicity of styrene had not been studied. However, according to a 1960 report [52], data on the acute animal toxicity of styrene had been published in Russia in 1936 by Larionov indicating changes in the lungs and bronchi, fat accumulation in the liver, and slight degenerative changes in the kidneys, as well as decomposition of leukocytes in the spleen, lymph nodes, and blood.

The first U.S. report of the effects of styrene was written by Spencer et al. [53] in 1942 who, based on animal studies, estimated that repeated exposure of workers to styrene at 650 ppm would produce no serious disturbances. However, it was noted that this concentration was definitely irritating to the eyes and nose and, therefore, the investigators [53] suggested 400 ppm as a tentative permissible limit for occupational exposure to styrene, a level producing a disagreeable odor but only slightly irritating.

Based on his experiences in the synthetic rubber industry, in 1943, Mallette [54] described styrene as a lung and skin irritant that produced light narcosis and possible liver and kidney injury. He noted that in a series of several hundred periodic examinations of the blood of workers in the rubber industry who were exposed to styrene, no traces of the "blood damage so characteristic of benzol" were found. Mallette [54] suggested that a styrene limit of 400 ppm was too high to prevent skin irritation among workers in synthetic rubber producing factories, and he stated that 200 ppm, which was not irritating to the eyes or nose, was preferable.

Case Studies and Miscellaneous Reports

Few cases of styrene intoxication as such have come to the attention of physicians because of obscure etiologies associated with styrene exposure, and there have been no reports of fatalities.

In 1946, McLaughlin [55] reported that among 458 chemical burns of the human cornea treated by him over a three-year period, thirty cases were caused by styrene. In the styrene cases there were only superficial transient disturbances of the eye, with return to normal within 48 hours in all but one case in which healing took three to ten days.

In 1952, Barsotti et al. [56] studied seven workers from a polystyrene manufacturing facility in Italy. The styrene concentration in the work area where styrene was loaded into the polymerization tower was reported as 188 ppm. Traces of styrene were found in the pumproom air, but no styrene was detected in any other area of the factory. Methods of sampling and analysis were not given. The workers had been employed in this factory for 18 months, and most had conjunctival and pharyngeal congestion. Two workers had an erythematopapular dermatitis localized on the back of the arms, with increasingly intense itching. Another had suffered for 3 months with a pruriginous dermatitis. Three workers had hyperactive deep reflexes. Complete blood counts and urinary hippuric acid concentrations were normal. None of 20 workers who handled the polymerized product had disturbances of any consequence. Atmospheric concentrations of polystyrene dust were not reported [56].

In 1964, Pratt-Johnson [57] described a case of retrobulbar neuritis in a 48-year-old self-employed Canadian who had worked for five years making reinforced plastics. The individual admitted that he had handled styrene carelessly, and had frequently come into contact with it with his bare hands. Initially, painless deterioration of vision to 20/400 and centrocecal scotomata were noted in each eye. Upon treatment with vitamin B compound and nicotinic acid for six months, visual acuity and visual fields improved slowly, recovery being complete within a year. The author [57] noted that circumstantial evidence alone incriminated styrene as the toxic agent. Kohn [58], in reviewing this study, stated "the likelihood of nutritional amblyopia could not be excluded."

In 1968, Matsushita et al. [59] described the case of a 35-year-old Japanese worker who developed symptoms of both central and peripheral nervous system poisoning while employed in a resin coating operation for 3.5 years. As a result of falling at work, he was examined by a physician who diagnosed his condition as organic solvent poisoning on the basis of progressive symptoms of peripheral numbness, fatigue, and dizziness, and work conditions. During a subsequent neurologic examination, a slight decrease in the muscular strength of the legs and arms, and the grasping strength of the right hand were found. Most reflexes were normal except for muscular reflexes of the upper limbs. Decreased sensation in the forearms and lower limbs was indicated by objective pain and vibration tests. Abnormal electromyograms (EMGs) of the arm and leg muscles were recorded and interpreted as indicating peripheral neuromyogenic nervous disorders. However, findings of normal motor nerve conduction velocities for ulnar, median, peroneal, and tibial nerves may not support this hypothesis. A slight contraction of the visual fields and a slight expansion of Mariott's dark point without eye fundus changes were found during ophthalmologic examination. No electroencephalographic abnormalities, indications of impaired liver function, or blood dyscrasias were found. The man was removed from work, treated as an outpatient, and slowly began to recover; however, about 22 months after treatment had begun, he was still hypersensitive to cold in his arms and legs. As a result of this case, the investigators [59] subsequently studied other workers in the factory and

determined that exposures were due primarily to styrene (up to 600 ppm) and occasionally to traces of toluene, ethyl acetate, and methanol. The results of this subsequent study are discussed in the Clinical Studies Section.

In 1971, a case of accidental exposure was reported by Schwarzmann and Kutscha [60]. In this incident a student inhaled some styrene vapor and spilled a "small" amount on his hand. Thirty minutes later the student noticed central blind spots in both eyes, and, 30 minutes after this, a headache developed. The blind spots had almost disappeared 1.5 hours after the initial contact, but the headache persisted and he was visibly shaking. He experienced hot and cold spells, had periodic sensations of numbness on the hand where styrene was spilled, and was extremely restless. For 7 hours following the accident, he felt very weak. After eating dinner he noticed the headache was gone. Other reports of this type of reaction to styrene have not been found, and many of the symptoms described could also be explained as hysteria or anxiety on the part of the student.

In 1971, Araki et al. [61] provided information of an 11-year history of lacrimation, nasal irritation, muscle soreness, headache, insomnia, general malaise, and anxiety, which led to the hospitalization of a 55-year-old man. The man had worked for 14 years in a Japanese factory where polyester resin tubs were manufactured. Although no information about airborne concentrations of styrene was given, the authors reported that the man typically handled styrene with his bare hands. As a result of this work practice, the skin on the man's hands was generally thin and atrophic. Biopsy revealed thinning of the prickle cell layer, flattening of the papillary layer, and marked edema with mild perivascular infiltration of the round cells throughout the dermis.

This case also had signs of neuropathy. Although pathologic reflexes were not found, he did have generally exaggerated deep tendon reflexes, paresthesia (tingling sensation) of the extremities, and bilaterally decreased cold sensation of the legs and feet. An electromyogram indicated a reduced number of motor units during maximal voluntary effort, and larger polyphasic action potentials of long duration. Biopsy of the biceps humeri and the gastrocnemius muscles revealed degeneration of the fibers with an increase of the sarcolemmal nuclei in some places. Biopsy of a peripheral nerve, n. suralis, showed no remarkable changes. The man's visual field and acuity were intact and an electroencephalogram (EEG) was normal. Since Raynaud's syndrome was absent and the man's symptoms were not consistent with scleroderma, Araki et al. [61] thought that the skin, muscle, and nerve changes were the result of the direct action of styrene and suggested, without explanation, that effects on the autonomic and central nervous systems were due to the action of styrene on the man's brain stem.

A chest roentgenogram of the man revealed pulmonary emphysema, but it was noted that the man smoked about 20 cigarettes a day. Hippuric acid excretion and results of tests of liver competence and blood counts were all normal, but creatinuria (0.187 g/24 hours) was noted. Araki et al. [61] also reported that about the time of the onset of symptoms (11 years prior

to hospitalization) the man was admitted to a hospital because of jaundice, but its cause was not established.

In 1973, Stepien [62] described the case of a 33-year-old female who suffered from thrombosis of the central retinal vein. She had worked over a year in a Polish experimental chemical laboratory and had been exposed mainly to styrene and solvents (not specified) in testing polyester laminates and epoxide films. Stepien [62] concluded that the interview, type of work, increased red blood cell count (RBC), toxic changes in the bone marrow, increased mandelic acid levels to 980 mg% ten days after last workplace exposure, and a lack of other reasons pointed to a toxic background for the disease, caused mainly by styrene.

In 1975, Hruba et al. [63] reported a study of two groups of workers from four Czechoslovakian plants; the styrene exposures were unspecified. The first group consisted of 101 workers who had been exposed to styrene for 2 months to 6 years; the other group, called a "control" group, included 21 workers just beginning employment. The most common subjective complaints of the 122 workers (95 women, 27 men, average age 35) were drowsiness (34%), headaches (28%), fatigue (25%), and increased irritability (14%). Examinations revealed signs of vegetative imbalance (64%), lowered tendon and periostal reflexes (19%), and slight signs of cerebellar nerve disturbances (14%). Normal EEGs were found in 13 of the exposed workers, borderline EEGs (including flat graph and conspicuous sleep activity) were found in 42, and mildly abnormal EEGs (including synchronous rhythms and centralized predominance of dispersed changes) were found in 46 of the 101 workers. Of the 21 workers in the "control" group just starting employment, 7 had normal EEGs, 7 had borderline readings (including mildly disturbed rhythm, increased beta, or flat graph), and 7 had slightly abnormal EEGs because of increased slow activity. After 3 years of employment, only 1 of the 21 "controls" had an EEG that the investigators [63] considered normal, 12 had borderline EEGs (including flat graphs and mildly increased sleep rhythms), and 8 workers had abnormal EEGs (not defined).

In 1974, Axelson et al. [64] described two men who were engaged in plastic boat production and had chronic emotional insufficiency with symptoms suggesting cerebral lesions around the time they started to work with styrene. TWA styrene concentrations measured at some worksites at one of the plants about a year after the men became ill were 200-292 ppm; instantaneous styrene peaks were sometimes higher than 1,500 ppm. There were some complicating factors, such as alcohol and drug abuse by one man, but these did not seem to the authors [64] to be of sufficient degree to have been likely causes. Axelson et al. [64] thought styrene might have contributed to the conditions, but believed the evidence was inadequate for a definite conclusion.

In 1976, Dowty et al. [65] reported qualitative analyses by gas chromatography and mass spectrometry of 11 paired maternal blood and umbilical cord blood samples obtained at birth. Styrene was identified in blood from both sources. The mothers were all healthy and 10 of the babies

normal. One infant with a lumbosacral meningomyelocele had numerous volatile organic compounds (apparently including styrene, acetone, and butylated hydroxytoluene) identified in the cord blood. The concentrations in these blood samples were not reported and are apparently not known. There were no known occupational exposures to styrene, and its sources were not determined.

In 1977, Holmberg [66] described CNS birth defects in children born to two women who were employed in factories in Finland where reinforced plastics were made. These two women were in a group of 43 women who responded to questionnaires sent to all women, without regard to their occupation, who had borne children with CNS defects in the previous year.

In the first case, the mother was a 19-year-old woman (first pregnancy, first birth). She and her 26-year-old husband, a carpenter, worked in a factory where reinforced plastics were made; her regular job was grinding, polishing, and mending reinforced plastic products. She was potentially exposed to styrene, polyester resin, organic peroxides, acetone, and polishes. At one point in her pregnancy (about the 4th month), she was "heavily exposed" to styrene for 3 days when she cleaned a mold. Her pregnancy was generally unremarkable, except for bronchitis during the 3rd month. The mother worked until 2 weeks before delivery. The baby, born in the 9th month, was 54 cm long and weighed 3,900 g. It had congenital hydrocephalus, anomaly of the right ear, and bilateral malformations of the thoracic vertebral column and ribs [66].

The other case involved a 24-year-old woman (first pregnancy, first birth) who also worked in the reinforced plastics industry. She was married to a 24-year-old welder-plater and gave birth to a 47-cm, 2,200-g girl. The child died during delivery and was anencephalic. The 7-month pregnancy was essentially uncomplicated although contractions that occurred in the 2nd month were controlled with 10 mg of isoxsuprine three times daily for 1 week. In the 7th month, the mother was treated for slight edema with 500 mg of chlorothiazide once daily for 1 week [66]. In the 3rd month, the woman was exposed to styrene, acetone, organic peroxides, and polyester resin while performing a hand-rolling operation for about 3 weeks with no respiratory protection. Afterwards, she was assigned to needlework in the same shop with occasional assignments in the hand-rolling operation.

Holmberg [66] reported still another case, not involving occupational exposure; it involved a 20-year-old woman (first pregnancy) who gave birth in the 7th month to a stillborn, anencephalic child. The mother was exposed to styrene on six occasions when her husband did repair work with reinforced plastics at home. The materials used were styrene, polyester resin, and organic peroxides. This case was complicated by a history of juvenile diabetes in the mother.

Based on information from the Finnish Register of Congenital Malformations, Holmberg [66] reported that the combined incidence of hydrocephaly and anencephaly among Finnish women of child-bearing age was

0.5/1,000 live births. He predicted 12 live births among women in the reinforced plastics industry during the 9-month study period, based on estimates of the number of women of child-bearing age employed in the Finnish reinforced plastics industry in 1974 (i.e., 250) and on Finnish fertility data. Thus, the normal combined rate of anencephaly and hydrocephaly (0.5/1,000 live births) was exceeded more than 300-fold.

Melgaard et al. [67] described chronic CNS changes in seven Danish workers, all males aged 42-65 years with a mean time of exposure to styrene of 15 years, ranging from 6 to 28 years. Exposure concentrations were not known, but the workers were all employed in small workshops with what were described as poor hygienic conditions. Details of the examinations were not provided except that neuroradiologic examinations were performed either with pneumoencephalography or computerized tomography.

The men had often experienced acute CNS effects (symptoms of acute intoxication with headache, dizziness, and a sense of drunkenness toward the end of the workday). At the time of examination in the hospital, they had complaints of fatigue, memory loss, difficulty in concentrating, unstated emotional complaints, and headache. In one man who had for several years imbibed alcohol excessively, there was biochemical evidence of liver damage and signs of polyneuropathy. Based on undescribed neuropsychological examinations, there was intellectual impairment in 6 men, 5 showed a moderate degree, and 1 was severe. Cerebral atrophy was found in 4 men by computerized tomography scan and in 1 man by pneumoencephalography.

Experimental Exposures

In 1944, Carpenter et al. [68] reported the results of an experimental study of two men exposed to styrene in a chamber at 800 ppm for 4 hours. The two men experienced eye and throat irritation immediately after entering the chamber. Increased nasal mucous secretion, a pronounced and persistent metallic taste, listlessness, drowsiness, and impairment of balance also occurred during this exposure. After exposure, symptoms of weakness, unsteadiness, inertia, and depression were reported. Urine collected over a 24-hour period from both subjects was analyzed for hippuric acid and neutral sulfur. In one subject, hippuric acid excretion was considerably increased. Neutral sulfur in the two subjects was increased by 17% and 48%, respectively.

In 1968, the effects of inhalation of styrene vapor at 51-376 ppm on human subjects were reported by Stewart et al. [69] . Nine healthy men were studied, some several times, in five experiments according to the design in Table IV-1.

TABLE IV-1

STYRENE EXPOSURE SCHEDULE

Experiment	No. of Subjects	Exposure Duration (h)	Styrene Concentration (ppm) Mean	Range
1	1	2	117	112-121
2	6	7*	99	95-107
3	3	1	51	50-55
4	3	1	216	203-236
5	5	1	376	368-403

*Two 3.5-hour sessions with an intervening 30-minute lunch period
Taken from Stewart et al. [69]

The styrene was 99.6% pure as determined by infrared (IR) analysis and contained 2 ppm of p-tert-butylcatechol to inhibit polymerization [69]. Styrene concentrations in the 12.5.xl.8x2.3-m (52.2-cu m) chamber were measured continuously with an IR spectrometer. The minimum detectable styrene concentration in the chamber using this method was about 11 ppm. Breathing zone samples, collected in 50-ml glass pipets every 10 minutes in experiments 1, 3, 4, and 5, and every hour in experiment 2, were analyzed by gas chromatography with a hydrogen flame detector. The minimum detectable styrene concentration by their method of sampling and analysis was 0.05 ppm. Total expired air samples were collected every 15 minutes and similarly analyzed during experiments 1, 3, 4, and 5 and every hour during experiment 2 by having the subjects breathe through a tube connected to a bag outside of the chamber. Urine samples were collected for 24 hours before the exposures and up to 2 days after the exposures for hippuric acid determination; urine samples from nine laboratory workers were used for comparison. Venous blood was collected in experiments 1, 2, and 3 during the final 10 minutes of exposure, and, in experiment 1, after 1 hour of exposure. Tests administered during exposure included a modified Romberg test (balancing on one foot with eyes closed and hands at side), heel and toe, finger to nose, the Crawford manual dexterity collar and pin test, and the Flanagan coordination test. Subjective and objective responses were recorded every 15 minutes during the exposures [69].

Two of five subjects exposed to styrene for 1 hour at 376 ppm reported eye irritation within 3 minutes; two more reported eye irritation within 15 minutes. All five subjects noted nasal irritation at this concentration. After 20 minutes, a burning sensation of the face was reported by one subject. After 25 minutes of exposure, one subject was unable to perform

the modified Romberg test normally. After 50 minutes of exposure to 376 ppm, two subjects exhibited decrements of 20% and 33%, respectively, in the Crawford manual dexterity collar and pin test, and three subjects dropped to a 10 percentile below their pre-exposure performance on the Flanagan coordination test. Nausea that occurred in one subject after 45 minutes of exposure persisted for 1 hour after the exposure. At the end of the exposure, two subjects reported feeling slightly inebriated; one of these subjects and one other individual who complained of headache performed the Romberg test abnormally [69].

After 20 minutes of a 1-hour exposure at 216 ppm, nasal irritation was noted by one of three subjects. Coordination and balance were not affected by this exposure [69].

During the 7-hour exposure at 99 ppm, two of six subjects noted mild eye irritation, and one noted mild throat irritation within 20 minutes after the exposure began. Eye irritation persisted for 30 minutes before subsiding, and the throat irritation subsided after drinking coffee. The Romberg test was performed eight times by each of the six subjects during this experiment. Two subjects perceived themselves as having difficulty performing the test on one occasion, and one subject perceived having difficulty on two occasions. The perceived difficulty was not reflected in the actual performance of the Romberg test, however, since Stewart et al. [69] stated there were no objective signs of impairment of balance during the seven hours. Performances on the Crawford dexterity and Flanagan coordination tests were also unaffected. Two subjects noted that the odor of styrene was faint, while the other four barely perceived it at the end of the experiment [69].

Although the odor of styrene was reported to be moderately strong by the subject in the 2-hour exposure at 117 ppm and by the three subjects in the 1-hour exposure at 51 ppm, no untoward subjective symptoms or objective signs of illness were reported [69].

Clinical laboratory test results that remained normal following each of the exposure sessions included complete blood count (CBC), sedimentation rate, reticulocyte count, serum glutamic-pyruvic transaminase (SGPT), lactic dehydrogenase, alkaline phosphatase, blood urea nitrogen (BUN), creatinine, and blood glucose. Urinary hippuric acid excretion was not significantly altered by the styrene exposures; pre-exposure values were 0.8-3.0 g/24 hours and the postexposure values were 1.0-2.9 g/24 hours. Styrene concentrations in exhaled breath samples during the exposures were 25% of the concentration present in the exposure chamber, which indicated about 75% retention. Concentrations of styrene found in the blood and postexposure alveolar air at the end of various periods are presented in Table IV-2. Percentages of absorbed styrene exhaled during various periods after removal from exposure are also given. After the exposure, only small amounts of styrene were eliminated in the breath; for example, 1.2% of the absorbed styrene was eliminated during the 4 hours after the end of exposure at 117 ppm [69].

TABLE IV-2

CONCENTRATIONS OF STYRENE IN CHAMBER AIR, POSTEXPOSURE VENOUS BLOOD, AND ALVEOLAR AIR

Exposure (h)	Styrene Concentration			Absorbed Styrene Exhaled in Postexposure Periods
	Chamber air (ppm	Blood (mg/liter)	Alveolar Air (ppm)	
1	51	0.2-0.7	1.0	0.7% in 7 h
7	99	0.9-1.4	1.3	0.7% in 2 h
1	117	1.7	-	-
2	117	2.7	1.8	1.2% in 4 h

Taken from Stewart et al. [69]

Hake et al. [70] exposed 10 men in groups of 2-4 for 1, 3, or 7.5 hours a day to 0, 20, 100, or 125 ppm styrene vapor. Eight women in groups of 1-4 were exposed at 0 or 100 ppm. Each subject was part of more then one group, but nonexposure weekends or control exposures (i.e., 0 ppm) were interspersed with the styrene exposures. For the men there were 3 days of exposure at 20 ppm, 4 days at 100 ppm, 4 days at 100 ppm with the concentration fluctuating between 75 and 125 to simulate workroom exposures, 5 days at 125 ppm, and 7 days at 0 ppm. The women were exposed to 100 ppm on 4 days and to 0 ppm on 2 days. The exposure chamber for control exposures was initially odorized by the introduction of styrene vapor at 10 ppm upon entry of the subjects, then reduced within 10 minutes to 0 ppm.

Daily check of the temperature and blood pressure, urinalysis, and continual medical surveillance during the study by a physician revealed no unusual abnormalities that could be attributed to exposures to styrene vapor; neither did the weekly battery of clinical chemistry tests. The weekly CBC did reveal that eight of the ten male subjects, after three consecutive days of exposure to 125 ppm, had elevated basophils in the differential analysis of blood samples drawn on the morning of the fourth day. The abnormal values ranged from 3 to 5%, the normal laboratory value being 0 to 1% [70].

No deleterious effect on equilibrium was found as measured by modified Romberg and heel-to-toe tests. There were some changes in 3 of 6 subjects in both visual evoked response and EEG amplitude over the course of the study deemed by the investigators [70] as consistent with CNS depression. However, the changes were neither uniform in all subjects identically exposed to styrene, nor were they consistent in magnitude within subjects.

Pulmonary ventilation (VE) values, forced vital capacity (FVC), fraction of FVC exhaled in one second (FEV_1/FVC), peak expiratory flow-rate (PEFR), and maximal mid-expiratory flow-rate (MMEF) in general showed no effects of styrene exposure. The investigators [70] stated that decrements in maximal expiration values, found in subjects repeatedly exposed for 7 1/2 hours to 100 ppm styrene, indicated a potential effect on pulmonary mechanics that needed further study.

There was no significant variance in cognitive testing scores because of styrene exposures. Electrically evoked electromyogram (EMG) configuration and latency between stimulus and response were found to be consistent throughout the period of study. The subjects were also asked to note on a checklist subjective symptoms during the experiment. The overall data indicated a dose-response relationship between two subjective symptoms, eye, nose, and throat (EyNT) irritation and headache. For the men, the incidence of EyNT irritation was 13% at 0 ppm, 17% at 20 ppm, 20% at 100 ppm, 33% at exposures fluctuating between 75 and 125 ppm that averaged 100 ppm, and 45% at 125 ppm; the incidence of headache was 3% at 0 and 10 ppm, 0% at 100 ppm, 13% at 100 ppm (fluctuating exposures), and 12% at 125 ppm [70]. There was no specific indication as to which exposure time (i.e., 1, 3, or 7 1/2 hours) the various subjective responses were elicited at a given exposure concentration. For the women, the incidence of EyNT irritation was 8% at 0 ppm and 32% at 100 ppm; the incidence of headache was 0% at 0 ppm and 35% at 100 ppm.

In 1974, changes in psychomotor function during styrene exposure were examined by Gamberale and Hultengren [71]. Twelve healthy men, 21-31 years old, were assigned to either of two groups of six. Each group was sequentially exposed to styrene vapor for four consecutive 30-minute periods at 50, 150, 250, and 350 ppm. The subjects, while at rest, inhaled styrene-air mixtures through a mouthpiece with very little breathing resistance. During the final 20 minutes of each 30-minute exposure period, tests of perceptual speed (numerical recognition and numerical sequence), simple reaction time, choice reaction time, and manual dexterity were given. At some point during each of the five tests, each subject's heart rate was recorded.

These same tasks were also performed under control conditions. To disguise the introduction of styrene into the exposure chamber and the changing concentrations of styrene, the authors [71] began the control experiments with a strong smell of styrene still in the mouthpiece, and ended with a 3-minute exposure to styrene. Upon completion of each 2-hour session, the volunteers evaluated their own conditions. Six pairs of contrasting condition descriptions were used: calm/hurried, active/passive, relaxed/tense, well disposed/ill disposed, unaffected/affected, and spry/tired. These were evaluated on 7-point scales in which point 4 described normal feelings and points 1 and 7 the extremes. At the end of the exposure, the subjects felt generally more tense and affected than under control conditions. None of the subjects believed that his performance on any test during exposure had been impaired [71].

There were no significant changes from control values in the manual dexterity or perceptual tests. However, there were changes in results of the reaction time tests. The differences between experimental and control values for simple reaction time increased throughout the exposure and with the increasing of the styrene concentrations. These differences were statistically significant only during exposure at 350 ppm styrene after consecutive 30 minute exposures each to 50, 150, and 250 ppm. The investigators did not employ an experimental design that allowed them to distinguish the effects of both exposure time and concentration [71].

In 1974, Oltramare et al. [72] reported their study of the toxicity of styrene in man. The study included experiments with six volunteers, three of whom had previous occupational exposure to styrene. None of the occupationally exposed group had worked with styrene during the 15 days prior to experimental exposure. Comprehensive physical examinations were given before the studies began.

The results of these examinations were within normal limits except for one case of slight anemia. The exposures were conducted in a chamber that was 2.6x2x3 m (15.6 cu m); styrene was introduced by blowing air from outside the chamber across a styrene vaporizer. The chamber was designed with an air intake vent in the ceiling that provided a slight air change in the chamber during exposure [72].

Forty-three exposure sessions (1-3 hours each) were held, using one to two subjects at a time. Two subjects were exposed to styrene once at 300 ppm, all six subjects were exposed one or two times at concentrations of 100 and 200 ppm, and most were exposed at 3-5 ppm and 50 ppm. For comparison, five of the six participants were exposed to toluene at 200 ppm, and two were each exposed to 1,1,2-trichloro-1,2,2-trifluoroethane at 300 and 600 ppm.

Psychomotor functions of the three subjects who had been occupationally exposed were studied with simple visual, audiovisual, and multiple stimuli reaction time tests. The subjects were individually exposed in sessions that lasted 90 minutes. All subjects were first exposed at 3-5 ppm of styrene to obtain control data. In other exposure sessions at least 1 week apart, the subjects were exposed in random order to styrene at 50, 100, and 200 ppm, and to toluene at 200 ppm. A final exposure session at 3-5 ppm styrene was conducted to obtain additional control data. One subject was not exposed to styrene at 50 ppm, and data from another subject were not obtained for toluene or the final 3-5 ppm session. At each session reaction times were determined before, 1 hour after start, and then 30 minutes after the exposures [72].

Simple visual reaction times measured during, and 30 minutes after exposure at 3-5 ppm were about the same as pre-exposure values. At 50, 100, and 200 ppm of styrene, reaction times lengthened by 12-37% during exposure as compared with pre-exposure values; half an hour after removal from exposure, reaction times in subjects exposed at 200 ppm were still increased 11-35% compared with pre-exposure values [72].

The audiovisual reaction time test required the subjects to push a button in response to either a green light or a sound. Results obtained during exposure were similar to those of the simple visual reaction time test, i.e., a drop in performance at exposures to styrene at 50, 100, and 200 ppm.

The multiple stimulus reaction time test consisted of three visual and two auditory stimuli. The 50 ppm styrene concentration had no effect on performance. The ability of the subjects to perform this diffuse attention test improved with repeated trials, both during each session and from the first session to the last. Thus, as the authors [72] commented, an effect of styrene at 50 ppm, if present, might have been masked by learning effects. However, decrements of about 2% were found during and after exposure to styrene at 100 ppm and of about 10% during and after exposures to styrene at 200 ppm. The functional significance of the decreases in performance found in any of the three tests was not discussed [72].

The authors [72] concluded that measurement of reaction time was a more sensitive method than vigilance tests for revealing slight effects of styrene on higher nervous system functions, and that styrene inhalation leads to narcosis. It is not evident whether the same conclusions on the relative merits of the two types of tests would have been reached had the investigators [72] controlled for the effect of learning rate or the order of presentation of tasks.

Equilibrium disorders (loss of balance) during styrene exposure were also investigated by Oltramare et al. [72] in three of the six subjects using a special platform for quantitative assessment of each subject's movements during performance of a modified Romberg test. In each 4-minute period, the number of movements was recorded. Statistically significant differences between results obtained from 1-hour exposures at 3-5 and 200 ppm and between 100 and 200 ppm were found, but no differences were found between results obtained at 3-5 ppm and those obtained at 100 ppm, suggesting a threshold between 100 ppm and 200 ppm at which performance of this test was impaired. However, due to the small sample size and the large dispersion of data, the authors [72] stated that the results should be confirmed with other experiments before drawing any definite conclusions.

Styrene in exhaled and alveolar air was measured in a series of experiments with a hydrogen flame ionization hydrocarbon analyzer, and the percentage of retained styrene was calculated. Usually two subjects were exposed together. To determine alveolar styrene concentrations, the subjects were asked to exhale normally into a plastic bag and then make a forced exhalation into a tube connected to a hydrocarbon analyzer. The average retention was about 64% of the inhaled styrene. A correlation coefficient of 0.88 was found between the styrene concentration in alveolar air during exposure and that in inspired air. Alveolar air concentrations were monitored for several hours after the exposures. At a given exposure concentration, the removal of styrene from alveolar air depended on duration of exposure. The fat content of the subjects was estimated from

anthropometric measurements; persons with the greatest estimated amount of fat had lower styrene concentrations in alveolar air and longer retention of styrene [72].

Urinary mandelate/creatinine ratios were elevated by statistically significant amounts ($p<0.05$) over control values in the two subjects studied after 90-minute styrene exposures. However, exposures for 90 minutes at 100, 200, and 300 ppm did not produce differences in mandelic acid concentrations that were large enough to distinguish between the exposures [72]. The six subjects were asked to note the occurrence of 12 symptoms during and after the exposures. From all of the experimental exposure sessions, a total of 55 reports of individual responses were available for analysis (Table IV-3). For each of the 12 symptoms in the table, the number of positive responses is presented as the numerator of a ratio. The denominator is the total number of individual reports for the exposure concentration. A given subject could have been tested more than once at a given concentration. For example, at 100 ppm there were 13 subject-exposures(denominator), gastralgia was experienced 3 times (numerator). It was not evident from the report whether one subject experienced gastralgia on three occasions or whether three different subjects experienced gastralgia [72].

TABLE IV-3

NUMBER OF TIMES SYMPTOMS REPORTED/NUMBER OF SUBJECT-EXPOSURES

Symptom		Styrene ppm 3-5	50	100	200	300
Irritation						
Lips	D	0/10	0/6	1/13	2/12	0/2
	P	0/10	0/6	0/13	1/12	0/2
Eyes	D	1/10	4/6	4/13	7/12	2/2
	P	0/10	0/6	1/13	2/12	0/2
Nose	D	4/10	3/6	7/13	5/12	1/2
	P	2/10	1/6	3/13	2/12	0/2
Gastralgia	D	0/10	0/6	3/13	5/12	1/2
	P	0/10	0/10	1/13	2/12	0/2
Nausea	D	0/10	0/6	5/13	4/12	2/2
	P	0/10	0/6	1/13	2/12	0/2
Dizziness	D	1/10	1/6	0/13	3/12	0/2
	P	0/10	1/6	0/13	2/12	0/2
Headaches	D	1/10	3/6	10/13	10/12	2/2
	P	0/10	2/6	8/13	9/12	0/2
Sleepiness	D	3/10	2/6	12/13	12/12	2/2
	P	1/10	1/6	4/13	11/12	2/2
Poor concentration	D	1/10	4/6	9/13	11/12	2/2
	P	0/10	2/6	4/13	9/12	2/2
Intoxication	D	0/10	1/6	2/13	6/12	1/2
	P	0/10	1/6	1/13	3/12	0/2
Fatigue	D	2/10	4/6	10/13	9/12	2/2
	P	2/10	4/6	9/13	9/12	2/2
Malaise	D	0/10	1/6	7/13	7/12	2/2
	P	0/10	0/6	1/13	0/12	0/2

D = occurrences during exposure
P = persistence after exposure

Taken from Oltramare et al. [72]

Symptoms indicative of narcosis and those referable to the digestive tract increased with increasing styrene concentrations. At 50 ppm, the investigators [72] reported that about half of the subjects experienced what was described as prenarcotic discomfort. The frequency of eye irritation generally increased with styrene concentration, but the other symptoms of irritation did not.

When subjects who had worked with styrene were compared with those without occupational exposure, it appeared that the styrene workers had become accustomed to some styrene effects. With the exception of symptoms of irritation, the symptoms noted were consistently fewer for the subjects with previous styrene exposures than for the other subjects. The workers previously exposed to styrene reported irritation at 3-5 ppm, and Oltramare et al. [72] considered that the greater degree of discomfort of the eyes, nose, and mouth may have been due to chronic inflammation from working with styrene. Oltramare et al. [72] also concluded that the nervous systems of the subjects with previous styrene exposure were either less sensitive than those of other subjects or that the subjects occupationally exposed to styrene in the past had become accustomed to the effects of styrene.

Subjects who had not been previously exposed to styrene complained of eye irritation, headaches, sleepiness, difficulty in concentrating, and fatigue when exposed at 50 ppm. When exposed at 100 ppm, they also complained of gastralgia, nausea, and malaise. The authors [72] cautioned that their studies were preliminary and based on an insufficient number of subjects.

In 1979, Odkvist et al. [73] reported the experimental study of five men, 22-34 years old, exposed to styrene at 300 ppm for 1 hour. The volunteers had no history that indicated disease of the nervous system, eyes, or ears. The exposure took place via a breathing valve during light exercise (50 Watts) on a bicycle ergometer with no significant electrocardiogram (ECG) changes recorded. The ability of the eyes to follow a stripe pattern (passing at a rate of 40 angular degrees per second) in an optokinetic test, immediately after styrene exposure, deteriorated in all five test subjects, although not significantly more so than in controlled experiments with no styrene exposure. No positional nystagmus, fixation nystagmus, or balance disturbance (standing on one leg with eyes closed and walking on a line with eyes closed) was observed in any of the test subjects. The mean concentration of styrene in the blood after 1 hour of exposure was 8.7 mg/kg. The authors [73] interpreted the deterioration of the eye's capability to follow an object as a styrene effect that decreased the inhibitory effect of the cerebellum on the motor function of the eyes.

Clinical Studies

Clinical studies of workers exposed to styrene can be classified by the relative extent to which effects are likely to be due to styrene. In the

production of polystyrene, occupational exposures are almost entirely to styrene. In plants that produce styrene monomer, there may also be exposure to benzene and ethylbenzene. In plastics applications such as reinforced plastics/composites (RP/C) where styrene is a solvent-reactant for copolymerization, styrene is the major air contaminant; however, there are concomitant exposures to fibrous glass, catalysts, accelerators, cleaning solvents, and other chemicals. In many of the RP/C applications, the operations involve potential contact of the skin with liquid styrene. During SBR production, workers are exposed to numerous ingredients and emissions (during vulcanization and curing) besides low levels of styrene. Thus, the likelihood that observed toxic effects are due to styrene exposure alone is greatest in the production of polystyrene, less in the production of styrene and reinforced plastics, and even less in SBR production.

(a) The Production of Styrene and Polystyrene

In 1963, an industry-wide retrospective study of morbidity with temporary loss of work among 1,240 workers from five Russian factories was conducted by Troshina [74]. Styrene, styrene-containing latex, polystyrene, and synthetic rubber were produced in four of the factories; styrene concentrations were not reported. In the fifth factory, products were made from polystyrene, which resulted in exposures to only "traces" of styrene. A comparison group consisted of workers with no styrene exposure from auxiliary shops in one factory. Only data from workers employed for at least a year were considered.

In general, liver and gall bladder illness were the main diseases recorded; Troshina [74] found that the morbidity rate among women was about twice that of the men. Details are presented in Table IV-4. Morbidity due to liver and gall bladder illness increased with increasing length of employment. However, due to the lack of exposure data, the cause of the reported effects is unknown.

TABLE IV-4

MORBIDITY DUE TO LIVER AND GALL BLADDER ILLNESS
IN WORKERS WITH EXPOSURE TO STYRENE

Factory	Percentage of Workers with Illness		
	Men	Women	Total
Styrene production	3.0	5.7	4.7
Production of styrene-containing latex	3.2	6.7	4.8
Polystyrene production	5.4	11.9	10.5
Fabrication of polystyrene products	0.0	0.7	0.5
Rubber production	2.6	4.0	3.3
Auxiliary shops (control)	1.3	2.0	1.5

Taken from Troshina [74]

In 1978, several clinical studies of workers in a styrene and polystyrene production plant in the Federal Republic of Germany were published by Theiss and Friedheim [75], Fleig and Theiss [76], and Theiss and Fleig [77]; Frentzel-Beyme et al. [78] also reported in 1978 on a retrospective cohort mortality study (which will be discussed in the Epidemiological Studies Section) at this same facility. Operations in the plant began in 1931, but what were described as considerable improvements in equipment and safety precautions were made about 1960. Only closed systems were in use at the time of the report. It is assumed that these changes led to a significant decrease in the styrene concentration, but comparative data were not given. Concentrations of styrene as high as about 50 ppm were found around some equipment. However, workers were seldom present in these areas. In areas where workers were frequently present, styrene concentrations in excess of 1 ppm were seldom found and were always less than 10 ppm. Styrene concentrations were determined in 1975 and 1976 by gas chromatography, and the techniques used had a lower limit of detection of 0.01 ppm styrene.

Mandelic acid concentrations in urine of the styrene-exposed workers were determined by the gas chromatographic method of Engstrom and Rantanen [79], as described by Schaller et al. [80]. Concentrations of mandelic acid in urine were less than 50 mg/l in 61 of 67 styrene and polystyrene production workers, and greater than 100 mg/l in 3 of the remaining 6. The data were presented only in bar graph form, and the maximum value was not reported. However, as will be discussed in a later section (see Figure V-1, p. 141), mandelic acid concentrations of 200 mg/l correspond to 8-hour TWA exposures of about 10 ppm.

In the morbidity study at this plant [75] there were 84 workers who had been engaged in styrene production for 1-36 years, 93 workers who had been engaged in polystyrene production for 1-38 years, and 62 control subjects with similar ages. In 1975-1976, the numbers of days lost through sickness were no greater for styrene and polystyrene workers than for all workers at the factory, and accident rates were no greater than for all production workers. There were no significant findings from examination of medical records or from physical examinations that included chest roentgenograms and measurements of vital capacity. Laboratory tests included CBC, thrombocyte count, measurement of activities of serum glutamic-oxaloacetic transaminase (SGOT), gamma-glutamyltranspeptidase (GGTP) (also known as gamma-glutamyltransferase), lactic dehydrogenase, SGPT, and alkaline phosphatase, measurement of total bilirubin, albumin, erythrocyte sedimentation rate, thymol turbidity, and creatinine and urea concentrations. Although unusual values were occasionally found among the test results, there were no statistically significant differences in the frequencies of their occurrence between the exposed workers and the unexposed controls.

Studies of chromosomes from lymphocytes of workers exposed to styrene at this German plant were reported in 1978 by Fleig and Thiess [76] and Theiss and Fleig [77]. A reference group of 20 men from the same factory, but not exposed to styrene, was used for comparison with each group of workers studied. Five workers engaged in the production of styrene had a slightly lower frequency of aberrant cells than the reference group (1.6% vs. 2.1%). Twelve workers who had spent 19-39 years in the production of polystyrene also had a lower rate of aberrations than the reference group (1.9% vs. 2.1%).

There have been a number of reports [58,81,82,83,84,85,86,87] on studies of workers in one U.S. plant that manufactured styrene and polystyrene. Sixty-five personal charcoal tube samples for organic vapors were collected during surveys in 1973 by Maier et al. [84]. All but 10 of the styrene concentrations were less than 5 ppm, and all but one were less than 20 ppm. Six benzene samples were in the range of 10-50 ppm, two were between 5 and 10 ppm, and 43 were less than 1 ppm with 34 of those being below the limit of detection. The highest concentration of ethylbenzene was 4 ppm. Except for 3 of 65 toluene samples being 212-262 ppm, toluene was present at less than 10 ppm. Acetone was present in 8 samples at 3-10 ppm. There were traces of pentane (used as a blowing agent) in 15 samples. The highest concentrations of styrene, benzene, and toluene resulted from spills and leaks. Of 34 detector tube samples, one indicated a high benzene concentration (30-60 ppm) and one indicated a high toluene concentration (300-400 ppm) after a spill of a benzene-toluene solution in the benzene building; the benzene concentration determined by a detector tube sample in this building the next day was 15 ppm [84].

One of the five samples of respirable dust (7.6 mg/cu m) measured in the polystyrene screening area was above the OSHA limit of 5 mg/cu m. Tricalcium phosphate personal respirable dust samples taken in the

polystyrene screening area contained 8.3 and 4.5 mg/cu m, respectively. Coal dust concentrations in the power house were 1.2, 1.8, 5.0, and 11.9 mg/cu m. The highest dust concentration occurred when fly ash was loaded into a truck. The sample of cadmium sulfide dust collected from the breathing zone of a worker who weighed cadmium sulfide pigments was 0.023 mg/cu m [84].

When the workers in this factory were studied in 1975 [58,81,82,83,85,86,87], environmental measurements were not made. However, environmental samples collected in early 1976 by the company and reported by Wolff et al. [85] indicated that exposures of styrene polymerization workers were similar to those found in 1973 by Maier et al. [84], and that exposures to styrene during copolymer production and styrene purification may have increased.

Styrene was not detected by spectrophotofluorometry (lower detection limit of 2 ng/l) in the blood of 244 of the 364 workers; the highest concentration found was 90 ng/ml [86]. By comparison, Stewart et al. [69] found 910 ng styrene/ml of blood in test subjects exposed for 7 hours at 99 ppm styrene, and Astrand et al. [88] found 300 ng styrene/ml of blood in test subjects exposed to styrene for 30 minutes at 50 ppm.

Various hydrocarbons in fat samples taken by needle aspiration were determined by gas-liquid chromatography and gas-liquid chromatography/mass spectrophotometry [87]. Styrene concentrations of 0.1-1.2 µg/g of fat were found in 13 of 25 workers, all 13 whose last exposure to styrene was 3 days or less before the fat samples were taken. No styrene was found in fat samples taken from the remaining workers whose exposure to styrene was either low or had occurred more than 3 days before the fat sampling.

Urinary mandelic acid was determined by the gas chromatographic method of Buchet et al. [89]. Mandelic acid concentrations were below the limit of detection (10 mg/g of creatinine) in 341 of 477 urine samples [86]. The highest mandelic acid concentration was 140 mg/g of creatinine. By comparison, Philippe et al. [90], using the same method, found mandelic acid at about 250 mg/g of creatinine in urine collected at the end of the workshift from workers exposed at 7-26 ppm. Other investigators [91,92] using other gas chromatographic methods found that a mandelic acid concentration of 140 mg/g of creatinine was associated with TWA exposures of workers to styrene at 7.5-15 ppm. In summary, the mandelic acid, and blood and fat styrene data [85,86,87] indicated that TWA exposures to styrene were probably less than 10 ppm.

Toluene was detected in 16 of 25 workers, but in measurable amounts of 0.2-0.3 µg/g of fat in only 3. Benzene was detected in three workers, but not in measurable amounts. Ethylbenzene was found in fat samples from 21 of 25 workers at concentrations of 0.1-0.7 µg/g. Although the workers were never exposed to ethylbenzene at airborne concentrations greater than 4 ppm, ethylbenzene was found in 84% of the fat samples, and traces were found as long as 90 days after exposure. A gas-liquid chromatographic peak that had

a retention time identical to that of 1-phenylethanol, a possible metabolite of both styrene and ethylbenzene, was found in the analysis of fat from all seven polymerization workers. However, the presence of 1-phenylethanol was not confirmed by other methods [87].

According to Maier et al. [84], company policy required that white blood cell counts (WBC) and hemoglobin and hematocrit determinations be made every 6 months for each worker in areas where benzene exposure was possible. Reports from the previous year were examined, and on eight occasions abnormal results consistent with benzene poisoning were found. However, when the individuals were retested, either these results were not confirmed or a cause other than benzene exposure was found. Based on their evaluation of the available medical information, Maier et al. [84] concluded that there was no evidence of chronic benzene effects among the workers.

Other investigators [81,82] conducted clinical studies on 494 workers from this plant. Styrene exposures were classified as high or low on the basis of job information and environmental data obtained from the employer [85] and environmental data reported by Maier et al. [84]. Hemoglobin concentrations in 14% of the workers were below 14 g/100 ml of blood; 3% had a WBC below 4,800 [82]. The low values were randomly distributed with respect to duration and extent of exposure. Activities of serum alkaline phosphatase, SGPT, GGTP, and SGOT, and the concentrations of serum bilirubin were determined. Only GGTP activity demonstrated a significant relationship to styrene exposure with about 3% of the values greater than 45 international units in low exposure workers and 7% in high exposure workers.

Lilis et al. [81] and Lorimer et al. [82] also studied effects on the nervous system. Prenarcotic symptoms had been experienced by about 10% of the workers in the low styrene exposure group and 19% of those in the high exposure group. Prenarcotic symptoms were reported most frequently by workers exposed more than 7 years. Among 412 workers who had no history of diabetes, back injury, or significant alcohol consumption, distal hypoesthesia (decreased sensitivity to touch) of the lower extremities and hypoactive deep tendon reflexes were found more frequently as duration of exposure increased. Distal hypoesthesia of the lower extremities was found in 4.1% of those who had worked 0.1-7.0 years, in 5.4% of those who had worked 7-20 years, and in 8.5% of those who had worked more than 20 years. Lilis et al. [81] did not differentiate between high and low exposure groups and did not say whether an effect of the workers' ages was considered. Because duration of exposure probably correlated with age, the effect might have been age-related rather than exposure-related.

Radial nerve conduction velocities were studied in 80 of the workers, and peroneal nerve conduction in 73 workers; workers with a history of diabetes, back injury, or significant alcohol consumption were excluded. Radial nerve conduction velocities of less than 55 meters per second (m/s) were found in 15 workers, but there was no relation to the duration or intensity of exposure to styrene. Peroneal nerve conduction velocities were

less than 40 m/s in 12 of 63 workers with more than 7 years of exposure and in none of 10 workers with less than 7 years. The mean peroneal nerve conduction velocities decreased with duration of exposure, but the decreases were not statistically significant and were not related to the intensity of exposure. Lilis et al. [81] did not give data concerning normal nerve conduction velocities, although it appears that neither 55 m/s for the radial nerve nor 40 m/s for the peroneal nerve is an abnormally low value, at least without making adjustment for age. The mean age of those with slower nerve conduction velocities was greater than that of those with velocities described as normal, but the age difference was not statistically significant.

Kohn [58] reported the results of a screening ophthalmological examination of 345 of the styrene-exposed workers. Styrene exposures averaged approximately 5 ppm. No evidence of optic neuritis or retrobulbar neuritis was found. Several workers gave a history of having had styrene beads embedded in their corneas, and one worker complained of beads embedded in the eyelid after a valve had burst. Conjunctival irritation related to styrene exposure occurred in 22% of the workers. The irritation was noted commonly at styrene concentrations above 50 ppm.

In respiratory system studies of these workers by Lorimer et al. [82], it was found that 19% of the high exposure group had experienced wheezing or tightness of the chest, compared with 7% of those in the low exposure group. These symptoms occurred weekly or monthly in about 12% of the high exposure group compared with symptoms occurring in about 5% of the low exposure group. However, spirometric studies of airway effects did not suggest significant changes, nor was there any radiologic evidence of significant lung change observed.

In 1971, Ponomareva and Zlobina [93] reported on workers in a Russian factory engaged in the production of block and emulsion polystyrene and styrene-acrylonitrile (SAN). The investigators examined 236 workers; 120 were engaged in the production of block polystyrene, 56 in emulsion polystyrene production, and 60 in copolymer production. Eighty percent of the workers were women, and most workers were 30-49 years of age.

The 120 block polystyrene production workers were divided into three groups: (I) those involved with the polymerization of styrene, where concentrations of styrene were occasionally as high as 5 ppm; (II) workers involved with polystyrene film and filament production, where they were exposed to styrene only 25-50% of the time at concentrations below 1 ppm, but at temperatures of 30°to 40°C; and (III) auxiliary and technical workers who had short, intermittent exposures to styrene (concentrations were not specified) [93].

The 56 workers involved in the emulsion production of polystyrene were also divided into three groups. Because styrene concentrations were usually below 1 ppm but polystyrene dust concentrations of 8-12 mg/cu m were frequent in the drying and packaging rooms, the groupings were based on

concentrations of polystyrene dust. The groups were: (I) workers engaged in polymerization, sedimentation, and centrifugation; (II) drying and packaging workers; and (III) a group of miscellaneous workers who experienced only brief contact with styrene vapor and polystyrene dust. Workers in Group I (polymerization) were occasionally exposed to styrene concentrations above 1 ppm. For the other groups, styrene concentrations were generally less than 1 ppm [93].

The 60 workers engaged in SAN manufacture were exposed to styrene at concentrations below 1 ppm. In certain operations the concentration of acrylonitrile exceeded 0.2 ppm [93].

In each case within the individual production units, it was those workers in the groups engaged in the polymerization process, i.e., groups designated I, who were exposed at the highest styrene concentrations. No additional information was presented about exposures, such as sampling and analytical methods, frequency of sampling, number of samples taken, or the number of workers in each subgroup.

Upon examination of the workers who complained of frequent sore throats, Ponomareva and Zlobina [93] found that most workers had a history of sore throats before employment at the facility. However, the frequency of this complaint increased after employment. About 29% of the workers from Groups I and II of the block polystyrene production unit and 21% of the workers from Group I of the emulsion polystyrene unit had tonsillitis with a high fever 4-8 times a year.

Workers involved in block polystyrene production had a significantly higher incidence of upper respiratory tract complaints than those workers who had only intermittent contact with either styrene vapor or polystyrene dust. Those workers with only occasional exposure to styrene vapor and polystyrene dust had a frequency of respiratory complaints no different from that of the population of the adjacent town. However, the incidence of respiratory complaints among the residents of the adjacent town was not reported, nor was the time of year when the study was conducted [93].

In the workers engaged in block polystyrene production for more than 5 years, there was a high frequency of dry, pale mucosa in the nose, the pharynx, and occasionally the larynx, which the investigators [93] thought might make these workers more susceptible to respiratory infection. These mucosal changes were found in 78% of those workers who had been exposed to styrene at 5 ppm periodically during their workshift (Group I), and among those workers exposed at less than 1 ppm for 25-50% of their workshift for more than 5 years (Group II). Ponomareva and Zlobina [93] speculated that high temperatures (30°to 40°C) contributed to the effects observed in the Group II workers. In some cases the mucosa was covered with a viscous muco-purulent secretion, and nosebleeds were reported. Ponomareva and Zlobina [93] diagnosed chronic inflammation of the nasal mucosa with atrophy of the mucous membranes in about 68% and chronic tonsillitis in about 39% of these workers.

Dystrophic upper respiratory changes similar to those found in the block polystyrene workers were found in about 45% of the workers in Group II of the emulsion polystyrene unit workers. Workers in the emulsion polystyrene production unit were found to have the mucosa of their noses and throats covered with polystyrene dust. However, there were fewer complaints in the emulsion polystyrene department, and fewer diagnoses of upper respiratory disease. The exception were workers of Group I where styrene concentrations were occasionally above 1 ppm [93].

High concentrations of polystyrene dust and elevated environmental temperatures may have been responsible for some of the health effects noted in the workers. In addition, the absence of any description of how the investigators assessed the working environment makes impossible an evaluation of this report in terms of the effect of styrene at various concentrations. The investigators [93] concluded that the workers who had the lowest exposure to styrene, heat, and polystyrene dust had a lower incidence of upper respiratory complaints.

In 1963, Zlobina [94] reported a study of 40 workers selected at random from two departments of a Russian polystyrene production facility. Styrene was the only contaminant present in significant amounts. In the block polystyrene production department, the styrene concentration (measured in the winter and summer of 1962) ranged from 0.5-2 ppm. The second department, emulsion polystyrene production, had styrene concentrations of 1-2 ppm; during the cleaning of process equipment, styrene concentrations frequently exceeded 12 ppm.

The morbidity rates, based on illnesses with absence from work, showed an increase in conditions ascribed to the liver and bile duct among workers in the two departments responsible for polystyrene production, compared with the rate for the entire factory (see Table IV-5). The lack of the diagnostic criteria used for determining liver and bile duct morbidity or information concerning the workers' personal habits, such as alcohol consumption, makes it difficult to interpret these results.

TABLE IV-5

MORBIDITY OF POLYSTYRENE PRODUCTION WORKERS
COMPARED WITH REST OF FACTORY

	Morbidity* (per 100 Workers)		
	1959	1960	1961
Total factory	1.7	2.7	2.1
Block polystyrene production	6.7	9.7	7.5
Emulsion polystyrene production	2.9	6.4	5.5

*Based on indicators of liver and bile duct disease
Taken from Zlobina [94]

The average blood pressure of twenty workers in the block polystyrene department was found to drop continually during the workweek from 105/65.7 to 93/57.5 mm Hg, while workers from the emulsion polystyrene production department exhibited a blood pressure decrease from 104.4/64.4 mm Hg to 92.8/57.2 mm Hg. Such changes were not seen in an undefined comparison group of workers similarly observed. When the workers returned to work after a day off, their blood pressures had returned to the initial values. However, the initial values were not reported, and it is not known why the systolic and diastolic pressures were so low. In addition, Zlobina [94] reported that 38% of the 40 workers had frequent headaches and subcostal (below a rib) pain on the right side, 44% expressed symptoms of irritation of the mucous membranes of the upper respiratory tract, and about 20% had pains in the epigastric and heart regions.

In 1975, Zlobina et al. [95] reported the results of a study of 110 women workers at a Russian polystyrene plant where the concentrations of styrene were about 1 ppm. Other volatile components were present in only trace amounts. The sampling and analytical methods used were not given. The investigation included a questionnaire, in-depth gynecological examinations, and inspection of individual clinic cards and birth histories. The control group was composed of 231 female workers in the plant management and children's group who had no previous industrial contact with chemical substances. To ascertain group comparability, the social-domestic factor was investigated by means of a questionnaire which included education, income, length of holidays, number of children, use of pre-school nurseries, time spent on housework, and time spent traveling to work. There were no significant differences between the groups of workers and controls on the criteria selected. Both groups were divided according to work experience and age.

An analysis of extragenital disease revealed a high incidence of gastrointestinal diseases (not specified) in the workers as compared to the control group. Gynecological examinations were given and there were no significant differences with respect to inflammatory diseases of the cervix or vagina, infertility, benign tumors, or deviation of internal sex organs. The styrene workers' incidence of inflammatory diseases of the uterus and appendages (12.7% vs. 4.7%) and the incidence of disorders in menstrual function (29.1% vs. 9.1%) significantly differed from the controls. Ten women complaining of disorders in menstrual function were examined by the colpocytological method which showed moderate estrogen insufficiency in five and pronounced insufficiency in two of them. No disorders in estrogen saturation were found in the other three women examined, although a hypermenstrual syndrome was observed in one of them [95].

The reproductive function of 67 female workers and 70 women in the control group was evaluated. There were no significant differences between the groups in the number of pregnancies, births, or induced or spontaneous abortions. Toxemias were more frequent in the first half of pregnancy in the experimental group (49.2% vs. 18.5%). Of the toxemias, nephropathy was observed significantly more often in the second half of pregnancy in the experimental group (10.4% vs. 1.4%).

In 1978, Veretinskaya et al. [96] examined hepatic function in 370 workers in three Russian polystyrene production plants. Industrial hygiene surveys at one of these plants 3 years after work began there showed that styrene concentrations varied considerably, but on the average did not exceed 1 ppm. Other workroom air contaminants were isopentane, benzaldehyde, benzene peroxide, and formaldehyde; all were within recommended concentration limits. The second plant had airborne concentrations of styrene stated as "not significantly exceeding 1 ppm." There were 20 workers examined from a third plant. This plant, since closed, had work conditions stated to be "unfavorable."

In the first plant, 22% of the workers had elevated bilirubin, caused in 50% of the cases by the free bilirubin fraction, in 30% by the conjugated fraction, and in 20% by an increase in both fractions. In a few cases (8%), beta-lipoprotein concentrations in blood serum were elevated. Studies of SGPT activities were unrevealing. Workers known to have hepatobiliary disease or to be alcoholic were excluded from testing. In the second plant, there were increases in beta-lipoprotein and SGPT, but not in bilirubin. However, while these changes were significant in terms of comparison with the control group, they did not exceed the physiological limits of variability [96].

In one shop in the third plant, 29% of the workers had bilirubin levels above normal limits and there was a slight and apparently insignificant number of workers with elevated levels of beta-lipoproteins. Enlarged livers were found in 6 workers, and pain in the area of the gall bladder was noted in 20% of those examined. In another shop in this plant, styrene concentrations had at one time exceeded the maximum permissible

concentration (MPC) of 1 ppm several hundredfold, but more recently styrene concentrations had been reduced in most places to less than the MPC. In this shop, there were elevated serum bilirubin concentrations in 20% of the examinees, elevated beta-lipoproteins in an unstated number (but not beyond physiologic limits), and an increase in SGPT in 13%. Leukopenia, stated to be a characteristic effect of styrene exposure, was found in 30% of these workers and in 18% of the controls; almost identical incidences of moderate leukopenia had been found in workers in the first plant and in their controls.

There were various effects attributed to functional changes in the liver. These changes did not reach pathological proportions in the majority of the cases; however, the changes suggested to Veretinskaya et al. [96] definite metabolic disturbances in the liver cells. The relationship of styrene to these effects is difficult to evaluate in this study because of the similarity in responses in areas with airborne styrene exposures believed almost always to be below the MPC (1 ppm) and in other areas with styrene exposures exceeding the MPC several hundredfold.

(b) Plastics Applications (Mainly Production of RP/C)

A clinical study of two factories in Czechoslovakia where reinforced plastics were made was reported in 1960 by Bardodej et al. [97]. In both facilities the styrene polyester resin was applied to wooden molds by hand; in one factory, however, the resin was sometimes sprayed on. Regular medical examinations (not specified) were given to the workers for a 3-year period.

Apparently, area rather than breathing zone air samples for the determination of styrene were collected on numerous occasions during an entire workshift in various work areas and analyzed by UV spectrophotometry [98], spectrophotometry after nitration [98], and polarography after formation of alpha-nitroso-beta-nitroethylbenzene [99]. The method of collection was not specified. The styrene concentrations found averaged about 50 ppm.

The investigators [97] measured benzoic acid and phenol in urine collected at the end of the workshifts from 58 workers and 23 controls. Elevated concentrations of substances measured as benzoic acid were demonstrated (800 vs. 400 mg/l). In a later publication, Bardodej and Bardodejova [100] stated that, with the analysis method used, both hippuric acid and mandelic acid were oxidized to benzoic acid. No increases in urinary phenols were found. There were no major medical findings in the RP/C workers except for four cases of dermatitis that were attributed to other agents. All but five of the workers reported developing increased fatigue and drowsiness toward the end of the workshift.

In 1972, Dzyuba [101] published the results of an investigation of a Russian reinforced plastics plant. Three groups of workers were evaluated over a 3-year period for neurological dysfunctions. Group I consisted of 70

concentration (MPC) of 1 ppm several hundredfold, but more recently styrene concentrations had been reduced in most places to less than the MPC. In this shop, there were elevated serum bilirubin concentrations in 20% of the examinees, elevated beta-lipoproteins in an unstated number (but not beyond physiologic limits), and an increase in SGPT in 13%. Leukopenia, stated to be a characteristic effect of styrene exposure, was found in 30% of these workers and in 18% of the controls; almost identical incidences of moderate leukopenia had been found in workers in the first plant and in their controls.

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In 1972, Dzyuba [101] published the results of an investigation of a Russian reinforced plastics plant. Three groups of workers were evaluated over a 3-year period for neurological dysfunctions. Group I consisted of 70

workers whose primary exposure was to styrene; Group II comprised 30 workers exposed primarily to phenol and aniline. Occupational exposure levels were not given. Fifty workers from an instrument manufacturing facility served as a control group. Results of these neurological examinations are presented in Table IV-6.

TABLE IV-6

RESULTS OF NEUROLOGIC EXAMINATION OF WORKERS EXPOSED TO STYRENE

Type of Findings	Percent With Positive Findings		
	Group I Styrene	Group II Phenol/Aniline	Controls
Subjective findings			
Constant headache increasing throughout the day with fatigue and sleepiness increasing after workshift	97	30	8
Nausea, dizziness, heart pain	66	20	2
Objective findings			
Emotional instability	91	60	10
Asthenia (weakness)	23	*	4
Cerebral nerve insufficiency	26	10	*
Unsteadiness in Romberg test	69	*	*
Finger tremors of extended hand	61	20	4
Increased tendon reflexes	100	33	16
Anisoreflexia	11	*	*
Sympathetic nervous system suppression	100	*	*

*Data was not given
Taken from Dzyuba [101]

Among Group I workers, a so-called asthenic-vegetative syndrome was observed in 22% in the first year, 64% in the second year, and 92% in the third year [101]. This neurasthenic syndrome was found in 52% of Group II (workers exposed to phenol and aniline) and in 5% of the controls. When the workers in Group I returned to work after having several days off, only a slight decrease in the manifestation of this condition was noticed, but it substantially decreased or disappeared in Group II workers.

In a factory in France where electronic filters for washing machines were produced, Bernard [102] in 1966 found evidence of blood abnormalities and CNS disturbances in workers. The filters were made by placing a resistor and a capacitor in a flexible plastic mold filled with a solution of polyester in styrene monomer. No information was presented concerning airborne concentrations at the time of the study, but after the introduction of ventilation equipment that changed the room air 50 times per hour, breathing zone concentrations of styrene were 40 ppm for workers who molded

parts and 100 ppm for those who removed the mold. Sampling and analytical methods were not described, nor were concentrations of trichloroethylene used as a cleaning solvent reported [102].

The workers encountered few skin problems, but used a skin cream to prevent skin dryness. There were, however, frequent reports of anorexia, asthenia (weakness), and headache. One worker also complained of nausea, vomiting, gastralgia, and vertigo. Subicteric conjunctivitis, slight leukopenia, neutropenia, lymphocytosis, and a slight anemia were found in this worker. Three other workers had severe anemia (red blood cell count (RBC) was about 3,000,000) that disappeared rapidly after the workers were given jobs away from possible styrene exposure [102]. Whether these effects preceded or followed installation of controls was not reported, though it seems likely that they were the motivation for the changes. Because of the absence of precise information concerning this sequence of events, this study cannot be used to help establish a recommended exposure limit.

Studies of four workshops in Sweden where reinforced plastics were produced were reported in 1972 by Gotell et al. [35] and by Axelson and Gustavson [103] in 1978. The 17 male workers studied had a median age of 28 years (range, 21-57 years) and duration of styrene exposure ranging from a few days to 12 years. Procedures used to manufacture reinforced plastic products involved coating wooden molds with wax, covering the molds with fibrous glass, and applying the styrene-modified polyester resin by either hand rolling or a combination of spraying and hand rolling. Based on their observations, Gotell et al. [35] judged the skin absorption of styrene under these conditions to be fairly low. The studies were conducted in the spring and fall so that the workers could be examined during moderate climatic conditions. Measurements were taken on a day in the middle of the week.

Styrene concentrations in the workers' breathing zones were determined by several methods. In two factories, the samples were collected for 30-minute periods in impingers containing ethanol and analyzed by gas chromatography; in another factory, air was sampled simultaneously by absorption in ethanol and analyzed by gas chromatography, by colorimetric indicator tubes, and by a combustible gas indicator. In the other factory, samples were collected for 24-66 minutes on charcoal and analyzed by gas chromatography. Although Gotell et al. [35] reported that some workers were exposed at 500-800 ppm for certain 1-hour periods, the 8-hour TWA exposure concentrations calculated for each worker ranged from 17-292 ppm. However, due to the nature of these processes, high concentrations of styrene vapor were often briefly encountered; in this study, concentrations of about 1,500 ppm were found for periods of 5-10 minutes. The workers were divided into three groups based on TWA exposures to styrene: (I) 235-292 ppm, (II) 89-139 ppm, and (III) 17-32 ppm.

All workers were given a brief neurological examination that included an evaluation of the knee and Achilles tendon reflexes, pupillary light

reflexes, and vibration sensibility; results of these tests were all normal. A modified Romberg test (one foot in front of the other) was given before and after work. Two workers showed a slightly unsteady Romberg test in the morning before work but not after exposure. A comparison group of 17 men from a motor workshop matched in age to the study group was used for the reaction time test. Reaction times of workers exposed to styrene at concentrations greater than 235 ppm were longer than those of workers exposed at less than 139 ppm and those of the age-matched control subjects, but statistical treatment of these data was not described. Differences between pre- and post-shift reaction time measurements were not significant in any group [35].

Lung function tests consisting of forced expiratory volume in one second (FEV_1) and vital capacity were normal in the morning and did not change during the day [35,103]. Blood samples were taken from 35 male workers in one plant, who had been exposed to less than about 100 ppm styrene. When compared with a group of 12 healthy males in a manufacturing industry, elevated levels of the liver enzymes aspartate-amino-tranferase (ASAT) and alanine-amino-tranferase (ALAT) were found in the styrene workers [103].

Complaints of irritation of the eyes and nasopharynx were common [35]. The concentration of styrene giving rise to these complaints varied from person to person. The tolerance to the irritant effects of styrene vapor may increase with exposure time, because workers complained of only minor to moderate irritation during exposures at 500-800 ppm for several hours, while the investigators [35] who were in the plant only during the study could not tolerate such concentrations for more than 1 or 2 minutes. It was also mentioned that several workers had quit their jobs because of dermatosis. Gotell et al. [35] speculated that the agents causing the dermatosis could have been the peroxide or cobalt compounds used as accelerators and catalysts.

In 1973, Bodner et al. [104] conducted a health hazard survey of a U.S. factory where reinforced plastic bathtubs were manufactured. The work involved spraying a fibrous glass-polyester resin mixture onto molds and then hand-rolling, laminating, and shaping. Although local exhaust ventilation was used in some of the operations, the makeup air was insufficient; thus, some workers wore respirators. Workers were exposed to styrene at 45-550 ppm as determined by breathing zone samples collected on charcoal for unspecified periods. In one operation where a foaming agent was sprayed, workers were exposed to methylene bisphenyl isocyanate (MDI) at 0.02-0.27 mg/cu m. The OSHA ceiling standard for MDI is 0.2 mg/cu m (CFR 1910.1000). Exposure to airborne fibrous glass was not measured.

Thirty-five workers (21 women, 14 men) were interviewed; their average age was 34 years. The average length of employment with the company was 3.7 years; however, this particular facility had only been operating for about 2 years. Sixteen of the workers (46%) smoked at least 1/2 pack of cigarettes a day. Four of the office workers, one man and three women, were used as a comparison group for the investigation. Complaints of some form of eye,

nose, or throat irritation were made by 34 of the 35 workers (97%) examined; 17 (49%) complained of wheezing, shortness of breath, or chest tightness, and 14 (40%) complained of skin rashes, hives, darkening skin color, or skin sores. Other complaints included nose bleeds, anorexia, excessive thirst, numbness of extremities, frequent headaches, occasional vomiting, and upset stomachs. None of these complaints were made by the four office workers who were interviewed for comparison. Since MDI was also present and is known to cause irritant effects similar to those observed among these workers, a direct attribution to styrene cannot be made.

In 1966, Simko et al. [105] reported the effects of styrene on 128 workers (101 women, 27 men) in three Czechoslovakian factories where reinforced plastics (chairs, small parts) were made. Average work experience was 1.8 years, with 20 of the workers having had more than 3 years of exposure. Operations were essentially the same in all three factories, and no respiratory protection was used. Styrene exposures in the three factories ranged from 4-195 ppm; methods of sampling and analysis were not reported. Table IV-7 presents the environmental styrene and urinary mandelic acid concentrations found.

TABLE IV-7

ENVIRONMENTAL STYRENE AND URINARY MANDELIC ACID CONCENTRATIONS

Factory	Year(s) of Exposure	Year(s) Measured	Styrene ppm	Mandelic Acid mg/l
I	5	1960-65	8-195	72-2,620
II	1	1965	5-165	80-2,100
III	1	1965	4-41	36-1,215

Taken from Simko et al. [105]

Clinical and neurological examinations of the workers at the beginning of the study included gynecologic examinations of the women and determinations of SGOT, SGPT, serum cholesterol, albumin, bilirubin, and urinary creatinine in all the workers. In factories I and II, where worker exposure to styrene was the greatest, all results from measurements of blood serum components were within normal limits; no signs of liver or gall bladder injury were found. The subjective symptoms reported included headache (20%), tiredness (15%), and drowsiness at work (13%). Hypertension was found in 23% of the workers. Simko et al. [105] concluded that the primary health hazard of styrene exposure was development of the

neurasthenic syndrome (a term not defined by the investigators), which was found in 33% of the 20 workers exposed to styrene for more than 3 years, and in 13% of the workers overall.

In 1962, Klimkova-Deutschova [106] reported neurological studies of 35 styrene-exposed workers (30 women, 5 men) in two Czechoslovakian RP/C plants. The workers had an average age of 38.5 years and an average exposure duration of 1.9 years. Styrene exposures in the two facilities were 43-131 ppm and 19-98 ppm. Dibutyl phthalate, trichloroethylene, and cobalt naphthenate were also present in the work environment. A catalyst, which was translated as being cyclohexyl peroxide, was also present. Methods of sampling and analysis were not reported. Workers were excluded in which earlier diseases such as hepatitis or working with other solvents could have played a role [107]. Each worker was given a clinical examination, and 17 had EEGs recorded.

The most frequent complaints were fatigue (41% of the workers), headaches (51%), and drowsiness with increased need for sleep (34%). Neurological effects reported included cranial nerve disturbances (91% of the workers), diminished reflexes (86%), and autonomic nervous system disorders (34%). Performance of a Romberg test (maintaining balance with eyes closed) and a Hautant test (walking with eyes closed) was impaired in 83% of the styrene workers. Of the 18 EEGs of 17 workers, 5 EEGs were judged to be normal [106].

A subsequent report in 1973 by Klimkova-Deutschova et al. [108] described findings in 21 workers examined for a period of three years from the start of exposure. The age distribution showed a marked predominance in the range of 40-49 years. The authors [108] found an increase in reports of fatigue, drowsiness, headaches, symptoms indicative of autonomic nervous system disorders, and hyporeflexia. Also, some workers had abnormal EEGs after 3 years of styrene exposure, whereas no abnormal EEGs were found during the pre-exposure examinations [108]. These effects were manifested in those workers with mandelic acid levels greater than 600 mg/l. Workplace exposure levels to styrene or other substances were not reported.

In 1967, Huzl et al. [109] reported an investigation of five separate RP/C facilities in Czechoslovakia. The average age of the 55 workers (34 women, 21 men) was 38.4 years; average exposure duration was 1 year. In four of the five facilities investigated, styrene polyester resin was applied by hand; the material was sprayed in the fifth facility. Only "primitive" engineering controls were in use in the four areas where the resin was spread by hand; gloves were used only occasionally. In addition to styrene, the workers were also exposed to cyclohexene peroxide, a resin catalyst, and to cobalt naphthenate, an accelerator. Styrene concentrations in the four hand lay-up facilities were found to be 47-94 ppm. In the fifth facility (spray-up), the ventilation was much better, and styrene concentrations were about 6 ppm. A comparison group examined in an outpatient clinic had previous occupational exposure to a variety of substances, including organic solvents, but not styrene. Medical histories

were taken and liver function tests performed. Based on urine specimens collected at the end of the workweek, Huzl et al. [109] found no simple statistical correlation between urinary mandelic acid levels and styrene exposure. However, Huzl et al. [109] believed that a urinary mandelic acid concentration greater than 300 mg/l indicated high occupational exposure to styrene. Mandelic acid values greater than 300 mg/l were found in 24% of the workers examined. The subjective complaints and objective findings of workers from the hand lay-up sites are presented in Table IV-8.

TABLE IV-8

SUBJECTIVE COMPLAINTS AND OBJECTIVE FINDINGS IN STYRENE-EXPOSED RP/C WORKERS FROM FOUR HAND LAY-UP SITES

Complaint or Finding	Percent of Workers	Percent of Controls
Headaches	36.4	21.8
Drowsiness, fatigue	23.6	20.0
Dyspeptic problems	10.9	*
Occupational eczema	7.3	*
Prolonged Weltman's reaction	48.1	23.6
Hyperbilirubinemia	17.1	*

*Data was not given
Taken from Huzl et al. [109]

Medical histories of the workers, according to Huzl et al. [109], revealed no cause other than styrene exposure for the prolonged Weltman's reactions noted, a nonspecific test which the investigators considered not necessarily indicative of liver disease. However, Huzl et al. [109] recommended that prospective workers with a history of liver disease and hepatitis not be allowed to work in areas with potential exposure to styrene.

In 1964, Zielhuis et al. [110] described a clinical study of workers in three factories in the Netherlands where reinforced plastic items (including boats, automobile bodies, and small objects) were manufactured. Boats were constructed using techniques in which layers of fibrous glass were impregnated by hand with a styrene-polyester mixture. The authors [110] noted that as the boats reached the final stages of construction, and the work area became more enclosed, the ventilation decreased. Workers had been exposed to styrene for 2-5 years. Breathing zone concentrations of styrene found during various operations in the factories, together with the authors' [110] classification of workers by job description, are listed in Table IV-9. However, precise information concerning methods of sampling was not provided by the investigators. Three groups of unexposed workers served as controls.

TABLE IV-9

AVERAGE STYRENE CONCENTRATIONS AT THREE FACTORIES

Factory	Group	Number of Workers	Worksite	Styrene ppm
A	Aa	5	Pilot plant Boat construction	24-94
	Ab	6	Pilot plant Laboratory worker	7
	Ac	5	Pilot plant Maintenance	Negligible
B	Ba	8	Steel Works Boat Construction	24-94
	Bb	8	Steel Works Car body construction	24-94
	Bc	22	Steel Works Small object construction	7
	Bd	21	Steel Works Upholsterers and steel workers	Negligible
C	Ca	6	Ship Wharf Boat construction	24-94
	Cb	5	Ship Wharf Carpenters	Negligible

Taken from Zielhuis et al. [110]

Although physical examinations (including blood counts, organ function tests, and urinalysis) revealed no abnormalities that could be attributed to the work situation, many of the workers in factories B and C reported having symptoms during their work with styrene. Workers' symptoms in factories B and C are presented in Table IV-10. Data reported in Table IV-10 were obtained through the use of a questionnaire given at the end of the shift on the days that the air samples were taken. The number of symptoms noted by the workers decreased with decreasing exposure. The authors [110]

concluded that a relationship existed between the workers' feelings of discomfort and styrene exposure. The most striking symptoms of discomfort were mucosal irritation and drowsiness. The workers reported that symptoms disappeared rapidly when they left the work area.

TABLE IV-10

SYMPTOMS OF WORKERS AT TWO PLASTICS PLANTS

Symptoms	Percentage* of Workers Reporting Symptoms Factory and Group				
	Ba N=8	Bb N=8	Bc N=22	Ca N=6	Cb N=5
Drowsiness	90	90	70	50	0
Apathy	70	70	50	10	0
Mental fatigue	50	90	30	0	0
Anorexia	70	30	10	50	0
Dizziness	30	70	10	50	10
Headache	70	30	50	30	30
Feeling groggy	10	50	10	30	0
Nervousness	30	10	10	10	10
Agitation	30	30	10	0	10
Nervous tension	50	30	50	0	10
Gastric pain	10	10	10	10	0
Tearflow	90	70	50	0	10
Eye irritation	90	90	50	90	0
Sneezing/coughing	70	30	30	70	10

*Actual value is the range of the tabulated value $\pm$10; e.g., 90 means that the percentage of workers reporting symptoms was between 80 and 100.
Taken from Zielhuis et al. [110]

In 1975, Gamberale et al. [111] studied 106 workers in four Swedish RP/C boat plants. Styrene-exposed workers included plastics workers and mechanics. The comparison group consisted of 36 workers in the same locality as two of the boat plants, not exposed to styrene. Styrene exposures varied from 10-120 ppm for the plastics workers and from 6-60 for the mechanics who were exposed at levels up to 312 ppm for 24 minutes, while working in narrow spaces.

Reaction time was measured by having the subject rest his wrist and forearm on a table, with his fingertips in contact with a pressure plate. The time between seeing a light signal and pressing the plate with the fingertips was the reaction time, expressed as the mean of 160 responses over a 10-minute period. Workers exposed to styrene had significantly longer reaction times than age-matched controls. This difference

was evident before work started in the morning, and showed a tendency to increase during the workday [111]. The data were not collected in a manner to allow inferences on concentration-response relationships to be made.

In 1977, Bergman and Lindberg [112] conducted industrial hygiene and medical studies at four Swedish factories where boats were made of fibrous glass-reinforced plastics. TWA styrene exposures ranged from 3-312 ppm for 39 of the workers with 29 of the workers having TWA exposures less than 100 ppm. Samples were collected with charcoal tubes or glass syringes and analyzed with a gas chromatograph. Interviews and medical examinations were given to 81 workers exposed to styrene and 32 workers with no styrene exposures. The 32 controls included some workers from other industries. Subjective symptoms elicited from the 81 styrene workers included fatigue that was not attributed to the heaviness or intensity of the work (60%), confusion or dizziness (38%), nausea (14%), headache (25%), and poor memory (21%). Only one of the controls mentioned any of the above subjective symptoms in connection with their work.

Rosensteel and Meyer [113] evaluated health hazards in a U.S. facility where reinforced plastic boats were manufactured. An initial survey in 1975 demonstrated that some exposure concentrations of styrene were greater than 100 ppm and that the workers were also exposed to acetone, methylene chloride, methyl ethyl ketone, naphtha, toluene, xylene, and asbestos. Twenty-one personal air samples in the lamination area were obtained in 1976 by the collection on charcoal for about 7 hours. TWA styrene exposures averaged 69 ppm and ranged from 9-111 ppm. These same workers also had average TWA exposures of 56 ppm acetone and 2 ppm methylene chloride (OSHA standards are 1,000 ppm and 500 ppm, respectively).

During one of the surveys, 9 of 14 workers interviewed reported symptoms of styrene exposure on the day of the interview, and all 14 stated that they had, at some time in this factory, experienced symptoms of styrene exposure such as eye and respiratory irritation [113]. These data are presented in Table IV-11.

TABLE IV-11

WORKERS WHO EXPERIENCED EFFECTS WHILE MANUFACTURING REINFORCED PLASTICS

Symptom	No. of Workers	Percent
Eye irritation	13	93
Skin rash	8	57
Nose irritation	7	50
Headache	7	50
Throat irritation	4	29
Chest pain	4	29
Dizziness	2	14
Fatigue/drowsiness	2	14
Cracked hands	2	14
Irritability/nervousness	1	7
Cough	1	7

Adapted from Rosensteel and Meyer [113]

During the last survey in 1976, serial detector tube sampling procedures were used by Rosensteel and Meyer [113] to determine 5-minute peak concentrations of styrene in workers' breathing zones; concentrations of 50-400 ppm were found. Analyses of samples collected during hull-stiffening, hull spraying, fibrous glass application, and hull roll-out areas, showed that styrene concentrations for 5-minute periods ranged from 200-400 ppm.

During the medical study, 41 workers were examined; 22 workers (16 men and 6 women with average ages of 28.7 years and 35.2 years, respectively) were from the lamination area. The other 19 examined for comparison were from other areas of the factory with little or no styrene exposure (13 men, average age 29.6 years; 6 women, average age 24.0 years). Workers from the lamination areas were matched with the control group on the basis of age, sex, and smoking history. However, because of the frequency of complaints of upper respiratory and eye irritation expressed by this group, perhaps from exposure to other irritants, their use as a comparison group may have been inappropriate. Air samples obtained over 6-7.5 hours from 10 of the 19 controls indicated TWA exposures to styrene below the level of detection for 6, 9-14 ppm for 3, and 62 ppm for 1. A medical history was obtained from each worker, and a physical and clinical examination of each worker was made. All results from blood analyses were within normal limits. Although the lamination workers had significantly elevated concentrations ($p<0.05$) of serum uric acid with respect to the comparison group, the levels were within normal limits [113].

At the time of the evaluation, all 22 lamination workers had work-related symptoms as did 55% of the comparison group. Subjective complaints that the workers reported occurring during their work with styrene and objective findings at the time of the study are presented in Table IV-12.

TABLE IV-12

SUBJECTIVE COMPLAINTS AND OBJECTIVE FINDINGS OF WORKERS WHO MADE REINFORCED PLASTICS

	Percentage of Workers With Complaints	
	Exposed	Control
Subjective complaints		
Eye irritation	45	26
Nose irritation	95	37
Nasal congestion	82	37
Cough	23	21
Chest tightness	23	16
Wheezing	18	5
Shortness of breath	54	11
Nausea and vomiting	0	0
Muscle weakness	4	5
Fatigue	36	5
Headache	14	5
Objective findings		
Skin rash	14	0
Conjunctival erythema	41	5
Nasal erythema	86	63
Mouth and throat erythema	45	32
Abnormal thyroid size	14	5
Rales and wheezes	9	0

Taken from Rosensteel and Meyer [113]

The average maximal mid-expiratory flow-rate (MMEF) of lamination workers that smoked was significantly less ($p<0.05$) at the end of the shift than at the beginning when compared with the smokers in the control group. Pulmonary function tests (FVC, FEV_1) did not reveal any other significant differences between styrene-exposed workers and those used for comparison. A number of suggestions were made concerning improvement of work practices and engineering controls; one recommendation made was that the workers in the high exposure areas be discouraged from smoking [113].

In 1968, Matsushita et al. [59] reported on 14 male production workers and 10 male office workers used as controls from a factory where plywood was laminated with a styrene-polyester resin. The men had been employed for 3-6 years; their average age was 29.8 years. Concentrations of styrene associated with different operations in the coating process ranged from 50-600 ppm; in other areas, no styrene was detected. Other substances including toluene normally were detected only in trace amounts. Toluene (50-550 ppm), ethyl acetate (3-160 ppm), and methanol (100-1,000 ppm) were present in the air when the equipment was cleaned daily during a 30-40 minute period; the workers took turns cleaning the equipment. The method of sampling and the number of samples taken were not reported. However, the substances were analyzed by gas chromatography.

Using questionnaires and interviews, it was found that all 14 of the styrene-exposed workers experienced throat pain, that 12 of them (86%) tired easily, and that 11 (79%) caught colds easily. Eye pain, bad breath during work, heaviness of the head, and feeling unwell during work were each reported by 10 workers (71%). Nose pain, headache, dizziness, palpitation and an oppressive sensation of the chest, anorexia, drowsiness during work, loss of weight, and severe forgetfulness were reported by 6-9 of the styrene-exposed workers (43-64%). Heaviness of the head (three complaints) was the most common complaint of the comparison group of 10 office workers; all other complaints were reported by only 1 or 2 of this group. While 8 of the styrene-exposed workers (57%) complained of decreased vision, ophthalmologic examinations confirmed this in only 4. Contracted fields of vision without fundus changes were found in 7. Twelve of the styrene workers were examined by a neurologist; increased knee jerk reflexes were found in 9, hyperreflexia of the Achilles tendon in 5, hyperreflexia of the upper limbs in 3, and sensation disorders in 4. Four styrene workers with severe symptoms were given EEG examinations; there were no abnormal findings. Three workers with severe symptoms had EMG abnormalities. Matsushita et al. [59] concluded that styrene had a major role in causing the effects found in these workers [59].

A series of reports by a group of Polish investigators [114,115,116,117,118,119,120] discussed results of studies of workers exposed to styrene during production of reinforced plastics. One group of 101 workers from two factories had been exposed for about a year; their styrene exposures in 1972 were about 25-75 ppm [115]. Twenty-one workers in another group had been exposed to styrene for about 10 years at concentrations that were about 75 ppm. Methods of sampling were not reported; analysis, however, was by colorimetric methods.

Urine samples were collected for determination of mandelic acid by the nonspecific, colorimetric method of Ohtsuji and Ikeda [121] for the same period during which the air samples were collected. Mandelic acid concentrations of up to 150 mg/l were considered normal, and concentrations greater than 400 mg/l were considered as definite indications of exposure to styrene. Urinary mandelic acid concentrations of the 101 workers who had been exposed for about 1 year (short-term workers) averaged 287 mg/l, with

concentrations of about 150 mg/l being found in 50 workers, 150-300 mg/l in 8 workers, and 300-494 mg/l in the remaining 43 workers [114]. The average concentration of mandelic acid in the urine of the 21 workers who had been exposed about 10 years (long-term workers) was 504 mg/l (range, 325-625 mg/l) [114,116]. Hippuric acid concentrations in the urine did not exceed the normal range [116].

In the 101 short-term workers, four cases of upper respiratory catarrh were noted by Chmielewski and Renke [114]. In 26 workers there were signs that the investigators classified as vegetative nervous system disturbances, which included skin marbleization, asymmetric body warming, prolonged blood vessel filling time, diaphoresis, excitability, hypoesthesia, whitening of fingers, trembling of hands, weakened reactions, cat's eye pupils, and nystagmus [115].

Clinical studies of these workers were performed that included blood cell and platelet counts [117]; examination of serum proteins, lipids, enzymes, bilirubin, and cholesterol [119]; glucose tolerance [116,120]; and 24-hour excretion of 17-ketosteroids [115,116,120]. Pulmonary function [114], blood clotting [117], and EEGs [118] were also studied in the long-term workers, and EEGs were studied in 43 of the short-term workers [118].

In the short-term workers, the significant clinical finding was that abnormal EEGs were noted in 31 of 43 examinations [118]. The abnormal EEGs showed discharges of sharp waves and high-voltage slow waves in the temporal regions that intensified with hyperventilation. Almost all short-term workers complained of "neurotic troubles." Signs such as intensified or abated deep reflexes, vestigial nystagmus, and tremors were interpreted by Dolmierski et al. [118] as being minor symptoms indicating that the nervous system was affected.

Average blood glucose in 53 short-term workers in one of the factories studied was lower than in a control group of 20 individuals [115,120]. Subsequently, blood glucose concentrations were studied in 40 workers in the other factory and in 18 controls using 50 g of glucose taken orally, followed by another 50 g of glucose taken orally 90 minutes later [115,120]. The results showed a heightened glucose tolerance in persons exposed to styrene. There was an indication that a tendency toward increased glucose tolerance was greater among 20 of the workers with concentrations of urinary mandelic acid greater than 400 mg/l and among 27 workers with a reduced 24-hour excretion of 17-ketosteroids (i.e., 5.78 mg/24 h on the average).

In another investigation of these same workers, Chmielewski [116] obtained somewhat different glucose tolerance test results from 21 long-term workers as compared to 40 short-term workers. The maximum concentration of blood glucose in the long-term workers occurred half an hour later on the average after administering glucose and did not rise after the second dose. The average response was due to three classes of blood glucose curves:

hypoglycemic, normal, and hyperglycemic. However, only the hypoglycemic workers responded to the second dose of glucose or to cortisone administered before the test. All workers had glucose assimilation coefficients below control values [116].

Other aberrant clinical findings in the long-term workers included reduced FEV_1/FVC in 4 of 21 workers examined [114], as well as reduced amounts of serum alpha- and beta-lipoproteins [119]. Twelve of the long-term workers had normal EEG patterns, two had borderline patterns, and four had abnormal patterns that were symmetrical in the temporal regions and characterized by low to medium voltage theta waves [118]. Most complaints by workers with abnormal EEGs were of fatigue, a sensation of weakness, and drowsiness. Compared with a nonexposed control group, the long-term group had a reduced number of blood platelets, an increased coagulation time, a reduction in prothrombin ratio, a shorter euglobulin fibrinolysis time, and an increase in blood platelet adhesion that was significantly correlated with beta-lipoprotein concentrations [117]. It was not mentioned whether the comparison group was age-matched to the exposure group, an important point in light of the comparison of serum lipoprotein levels between short-term and long-term workers; thus, the effect of age on these comparisons is not clear.

Occupational dermatoses were reported in 1975 by Golebiowska-Podgorczyk [122] among 70 workers in a Polish factory where boats were built from fibrous glass-reinforced plastic. The workers ranged from 20-64 years of age and had worked at this factory for 1-15 years. The group studied was composed of 15 carpenters, 37 molder-artists, 13 iron workers, and 5 unskilled laborers. The workers were exposed to a variety of polyester resins dissolved in styrene, epoxide resins dissolved in acetone or ether, hardeners that included cyclohexanone hyperoxide, dibutyl phthalate, methyl ethyl glycol hydroxide, and triethylenetetramine, cobalt naphthenate, organic dyes, and various glues. No industrial hygiene monitoring was conducted. None of the workers had a history of, or a predisposition to, any allergic disease, but 18 experienced some type of dermal trauma as a result of their employment. Three of these 18 worked with fibrous glass. No positive reactions to styrene or polyester resins were found by patch testing, although positive reactions were found to the epoxide resins and some of the hardeners. Golebiowska-Podgorczyk [122] found four cases of excessively dry, chapped, and cracked hands and suggested this might have been caused by the defatting action of styrene.

In 1978, Rosen et al. [123] reported, in what was described as a pilot study, the results of neurological examinations of 33 workers from 3 different worksites in Sweden. Thirteen of the workers (aged 24-66 years) had been employed for 1-21 years in the polyester resin boat industry (Group I). Exposures to styrene had been measured the previous year and averaged 125 ppm (range 74-175 ppm), but Rosen et al. [123] stated that during previous years the exposures were significantly higher. Ten of the workers (aged 23-54) had been involved in the production of polyester resin cisterns for 2-14 years (Group II); their average exposure based on measurements

taken 2 years earlier was 47 ppm styrene. The remaining ten workers studied (aged 29-65) were exposed to less than 5 ppm styrene while producing polystyrene for 5-15 years (Group III).

Results of the study were compared with two "control" groups. One group (called the "normal" group) consisted of six men from a hospital transportation service never significantly exposed to organic solvents; the other group (called the "reference" group) consisted of 17 men, many of whom were former painters, reported to have signs of chronic intoxication due to exposure to a mixture of organic solvents. All examinations of styrene workers were performed at least 48 hours after the last exposure, to avoid possible acute effects of styrene on the results. The reported incidences of unusual tiredness, reduced short-term memory, giddiness, headache, paresthesia in fingers or toes, conjunctivitis, throat irritation, and a minor decrease of muscle stretch reflexes were higher in the styrene-exposed workers than in the "normal" group. These results were roughly dose-dependent with the reported effects occurring most among the workers in the higher exposure group (I), but also frequently occurring in the medium exposure group (II), and occasionally among the polystyrene workers, who had the lowest styrene exposures (Group III).

Signs of polyneuropathy or CNS lesions were not found in the styrene-exposed workers. Motor conduction velocities of median, ulnar, fibular, and posterior tibial nerves were recorded, as well as sensory action potential of the median and ulnar nerves. An EEG examination was made while the subjects were awake, and included studies of the effects of arousal, hyperventilation, and intermittent light [123]. No differences in motor conduction velocities were found between the groups. Ten of the 33 styrene-exposed workers had evidence of a mild sensory neuropathy with polyphasic sensory responses of a low amplitude; a similar pattern was found in many of the workers in the solvent-exposed "reference" group. The 10 affected styrene workers were more heavily exposed than those not having signs of neuropathy, but they were also older and had more years of exposure. Based on corrections for age published by others, the investigators [123] believed that age alone could not have accounted for the effects, but speculated that the effects of age and styrene exposure may have been synergistic. Eight of these ten workers had EEG changes consisting of fast activity within the rostral and central parts of the hemispheres; similar changes were common in the solvent-exposed "reference" group, but were seen in only one of the other 23 styrene-exposed workers. Unexpectedly, the highest frequency of diffuse slow activity over both hemispheres was seen in those workers (Group III) exposed at the lowest styrene concentrations. The investigators [123] suggested that the additional exposure of Group III to isopentane might be relevant, but no isopentane determinations were made.

In 1976-1978, a series of reports [124,125,126,127,128] were written by a group of Finnish investigators who examined the results of psychological and neurophysiological tests of 96 workers from 24 different factories where reinforced plastics were made. The workers were 16-54 years old

(mean age, 29.6) and had been exposed to styrene for as little as 6 months or as long as 14 years (mean duration, 5 years). Styrene exposures of these workers who used their hands to spread polyester resin, were evaluated from urinary mandelic acid concentrations determined by the colorimetric method of Ohtsuji and Ikeda [121] in about half of the workers, and by the gas chromatographic method of Engstrom and Rantanen [77] in the remainder. Results from the two methods were transformed to a common scale [79,127]. Urine specimens from each worker were collected at the end of an 8-hour workday, once a week, on a different day each week for 5 weeks. The mean of the five determinations of mandelic acid was used as an index of exposure for each individual. The range of the individual means was 7-4,715 mg/l; the group median was 808 mg/l.

Neurophysiological findings of these workers were reported by Seppalainen and Harkonen [124], psychological functions and data relating to alcohol consumption were reported by Lindstrom et al. [127,128], and effects on the nervous system were reported by Harkonen [126] and Harkonen et al. [125]. EEGs were recorded for all 96 of the workers at least 20 hours after the last exposure to styrene. The recording period lasted 30 minutes, and a 3-minute hyperventilation and a photic stimulator were used as EEG pattern activators. All EEGs were interpreted by one investigator who had no knowledge of the subjects' exposure histories. The findings were normal in 73 of the workers. Abnormal EEG patterns were found in 23 workers with 14 having local slow activity, 8 with diffuse theta activity, and 2 with bilateral spike and wave discharges (1 worker had 2 abnormalities). Based on the available literature on EEGs, about 10% abnormal patterns were expected by the investigators [124] for a normal population. The incidence of abnormal EEGs found (24%) was significantly greater ($p<0.01$) than expected. Of the 23 workers who had abnormal EEGs, 19 had urinary mandelic acid concentrations greater than 700 mg/l. In a subsequent analysis of the data, Harkonen et al. [125] presented evidence that this concentration of mandelic acid corresponded on the average to an 8-hour TWA styrene exposure of 31 ppm.

Possible peripheral nerve dysfunction in 40 of the workers (average age 29.6 years) in the study group with the most severe complaints was also investigated by Seppalainen and Harkonen [124] using nerve conduction velocity measurements. Thirty healthy, age-matched men with no history of occupational exposure to toxic chemicals were used for comparison. An electromyograph was used to measure maximal motor conduction velocity of the median, ulnar, deep peroneal, and posterior tibial nerves; conduction velocity of slower motor fibers of the ulnar and deep peroneal nerves; and the sensory conduction velocity of the median and ulnar nerves. There were no statistically significant differences between the styrene-exposed workers and the comparison group in average nerve conduction velocities. However, slightly abnormal conduction velocities were found in 9 of the 40 workers; the criteria used for judgment were not stated. Five of these workers displayed mononeuropathy, and the other four exhibited polyneuropathy. In four of the workers with mononeuropathy there were possible causes other than styrene exposure; in the fifth worker, no other cause for the

neuropathy could be found. In three of the workers with polyneuropathy, no cause other than styrene exposure could be found. There was no association between urinary mandelic acid concentration and nerve conduction velocity in the four subjects with unexplained abnormalities.

To study psychological functions in these workers, Lindstrom et al. [127] selected a comparison group of 43 men who worked with reinforced concrete. The comparison group was similar to the styrene-exposed group in age distribution, educational level, and geographic location. Psychological functions which were measured by 30 tests included general intelligence (5 tests), visuomotor speed (8 tests), visuomotor accuracy (3 tests), memory (5 tests), vigilance (2 tests), psychomotor performance (3 tests), and personality (4 tests). Comparisons were made between averages of RP/C workers and the comparison group scores. When comparing these two groups, performances on two tests, one a measure of visuomotor accuracy and the other a measure of response time in Rorschach inkblot tests, were significantly impaired ($p<0.05$) in the RP/C workers. When the 19 styrene-exposed workers with urinary mandelic acid concentrations greater than 1,762 mg/l were compared with the 36 workers who had urinary mandelic acid concentrations less than 674 mg/l, greater visuomotor inaccuracy and poorer psychomotor performance were found in the workers with the higher mandelic acid concentrations. Step-wise multiple regression analyses were used to study relationships of variables to urinary mandelic acid concentrations, duration of exposures, and the combination of mandelic acid concentration and duration of exposure. Duration of exposure had only a slight relationship to disturbances in psychological functions. One measure of visuomotor speed and one measure of visual memory correlated with the duration of exposure; their joint partial correlation with duration of exposure, when the effect of age was eliminated, was 0.28 ($p<0.05$). High urinary mandelic acid concentration was related to visuomotor inaccuracy ($p<0.01$), and it had a slight relationship to vigilance and psychomotor performance ($p<0.13$). The product of duration of exposure and urinary mandelic acid concentration was related to visuomotor inaccuracy and one Rorschach variable, long latency time in answering.

For the study of subjective symptoms experienced by these workers, Harkonen [126] selected a comparison group of male postal workers and electricians (mean age, 29.3 years) with no reported previous exposure to styrene. Both the workers and the comparison group were requested to complete questionnaires dealing with subjective symptoms felt during the workday. In contrast to the comparison group, the styrene-exposed workers felt tired more often in the morning and excessively tired after work, and they also reported more difficulties in concentrating and more frequent loss of appetite. During the workday, the RP/C workers frequently experienced irritation of the eyes, nose, and skin, and many felt nauseated and intoxicated. No correlation was found between urinary mandelic acid concentrations and the magnitudes of the symptoms scored on a scale of 1-3. Harkonen [126] suggested that no correlation was found because acute symptoms may be associated with peak exposures, whereas mandelic acid concentrations reflect the average exposure of the day.

In 1978, Harkonen et al. [125] summarized these studies [124,126,127] and extended some of the analyses. By plotting the log of the urinary mandelic acid concentration against the log of the 8-hour TWA styrene concentration, a significant correlation ($r=0.92$, $p<0.001$) was found. A urinary mandelic acid concentration of 700 mg/l corresponded to 31 ppm of styrene, 800 mg/l to 36 ppm, 1,200 mg/l to 55 ppm, and 1,600 mg/l to 74 ppm. Urinary mandelic acid concentrations were related to the percentage of EEG abnormalities in the group. Repeated slow wave activity and bilateral spike and wave discharges were used to indicate EEG abnormalities. In 38 workers whose urinary mandelic acid concentration was less than 700 mg/l, the percentage with abnormal EEGs was comparable with the general population (about 10%). Of 58 workers with mandelic acid concentrations greater than 700 mg/l, about a third exhibited EEG abnormalities. There was a significant degree of visuomotor inaccuracy with the symmetry of drawing test in workers whose mean urinary mandelic acid concentration was 800 mg/l. However, using the Bourdon-Wiersman test, visuomotor inaccuracy was statistically significant ($p<0.05$) only when the mean mandelic acid concentration was greater than 2,000 mg/l. A statistically significant decline in psychomotor performance (Mira Test) was found at mandelic acid concentrations greater than 1,200 mg/l (equivalent to about 55 ppm styrene). Harkonen et al. [125] concluded that although visuomotor accuracy and unimpaired psychomotor performance may be important in certain demanding operations and a prerequisite for safety at work, impairment may not necessarily affect a worker's performance under normal conditions, but may have an indirect impact by demanding more adaptation and more energy for compensation.

Lindstrom et al. [128] interviewed these same styrene-exposed workers about their alcohol consumption. A quantity of alcohol sufficient to produce a slightly intoxicated state was consumed daily by 1 worker, twice weekly by 22, once or twice a month by 56, and less frequently by the other 19 workers. Frequency of alcohol consumption for the group was about the same both before and after styrene exposure began. Decreased tolerance to alcohol was reported by 32% of the workers, about the same as in a comparison group of painters exposed to other solvents, but greater than in a group of railroad workers having no reported solvent or styrene exposure.

The amount of, and changes in, alcohol consumption and decreased tolerance to alcohol were not statistically related to the duration of exposure to styrene or to the concentration of urinary mandelic acid [128]. Overtime work, another index of styrene exposure, was related to alcohol consumption. The workers with high alcohol consumption were characterized as having straying thoughts and difficulties in staying asleep. Hand tremors and tiredness were related ($p<0.05$) to both the amount and frequency of alcohol consumption. Of all psychological functions, only lowered visuomotor speed was related to the amount of alcohol consumed [128]. Visuomotor inaccuracy was not the function that was previously related to high styrene exposure by Lindstrom et al. [127]; thus, Lindstrom et al. [128] concluded that the psychologic symptoms and signs related to alcohol behavioral variables were not related to styrene exposure.

In 1977, Meretoja et al. [129] reported an increase in the rate of chromosomal aberrations of the lymphocytes in peripheral blood. The ten men studied were 20-41 years old and from a Finnish factory where polyester plastic laminates were made. These workers had been exposed to styrene for 0.6-8.5 years. Before testing began, a complete health history was taken from each worker, followed by clinical and psychological examinations. No previous or present evidence of diabetes, epilepsy, or periods of unconsciousness lasting more than 30 minutes was found in any worker. Five healthy men with no known exposure to styrene or to any agent with known clastogenic activity were used as a comparison group.

No industrial hygiene sampling was conducted, but urinary mandelic acid concentrations were determined from specimens obtained at the end of an 8-hour shift to evaluate styrene exposure. A record was made of past exposures to any known clastogen, and a CBC was also performed [129]. The chromosomes of lymphocytes from peripheral blood of the styrene-exposed workers and the comparison group were studied. At the time of study all the workers were reported to be in good health. Results are presented in Table IV-13.

TABLE IV-13

ANEUPLOIDY AND CHROMOSOMAL ABERRATIONS
IN THE LYMPHOCYTES OF STYRENE-EXPOSED WORKERS

Subject No.	Age Yrs.	Years of Styrene Exposure	Mandelic Acid *	Interphase Cells: Micronuclei **	Interphase Cells: Nuclear Bridges **	Aneuploidy ***	Polyploidy ***	Chromosomal Aberrations ***
				Plant 1				
1	24	0.7	833	8	5	2	-	11
2	20	0.6	229	7	2	4	-	11
				Plant 2				
3	21	1.5	3,257	14	8	2	-	26
4	37	8	23	9	3	3	-	25
5	41	2.5	219	12	0	5	-	13
6	27	2	1,452	6	3	7	-	15
7	21	1	422	6	4	6	1	16
				Plant 3				
8	32	8.5	75	7	0	3	1	17
9	23	3	645	12	6	5	2	17
10	26	4	55	7	11	4	-	15
				Comparison Group				
11	32	0	0	2	0	1	-	2
12	35	0	0	0	0	3	-	4
13	33	0	0	0	2	3	-	1
14	30	0	0	2	2	1	2	1
15	30	0	0	0	0	2	-	1

*mg/g creatinine in urine
**Aberrations/1,000 interphase cells
***No./100 metaphase cells
Taken from Meretoja et al. [129]

There was a statistically greater incidence ($p<0.001$) of cells with chromosomal aberrations in lymphocytes of workers who had been exposed to styrene than in the comparison group (16.7 vs. 1.8 cells, on the average), but the biological significance of this difference is not known. An

increase in the frequency of micronuclei and nuclear bridges between cells was also observed. The incidence of aberrant cells ranged from 11-26% in the lymphocytes of the styrene-exposed workers and was only 1-4% in the lymphocytes of the unexposed comparison group [129].

In a related study in 1978, Meretoja et al. [130] examined the lymphocytes from the peripheral blood of 16 workers (which included 8 workers from the previous study [131]) exposed to styrene in two reinforced plastics factories. No data was given regarding occupational exposures. The subjects, all men 21-51 years of age, had been employed mainly in laminating work for 1-15 years. A statistically significant increase ($p<0.001$) in the incidence of chromosomal aberrations, mainly breaks, was found when compared to the comparison group (15.1 vs. 2.0%), and this was confirmed when 10 of these 16 workers were reexamined a year later and the incidence was 16.2%. The comparison group consisted of six men from outside the factory environment. However, the frequency of sister chromatid exchanges (SCE) was not significantly increased in these styrene workers (5.3 vs. 4.4 SCE/cell in the comparison group). SCE reflect intrachromosome rearrangements of the DNA helices, and as such are a sensitive indicator of damage to the DNA.

In 1979, Hogstedt et al. [131] also found an increased frequency of chromosomal aberrations among reinforced plastics workers in Sweden. Six male workers from a plant manufacturing polyester resin boats, aged 21-56 years with a mean age of 33, were matched by age and sex with 6 workers from a nearby paper factory without exposure to chemicals. In the plastics workers, there was an average of 10.8 aberrations per 100 cells in chromosomes from venous lymphocytes, a statistically significant increase ($p<0.001$) over that in the reference group, 5.2/100 cells. There was also an excess in gaps (3.2 vs. 2.4/100 cells, not significant), isochromatid and chromatid breaks (6.9 vs. 2.5/100 cells, $p=0.008$), and hyperdiploidy (0.7 vs. 0.3/100 cells, not significant). Airborne TWA styrene concentrations measured in previous years ranged from 14-73 ppm, with occasional concentrations as high as 188 ppm, for short periods of time. The investigators [131] speculated that, although styrene was the probable cause of the changes, exposure to other chemicals might have contributed; information was not given on these "other" chemicals.

In 1980, Andersson et al. [132] studied 39 men occupationally exposed to styrene in a plastic boat factory. The total exposures of these workers over a 6-year period were measured with personal TWA samples analyzed by gas chromatography and expressed as a concentration multiplied by the number of years of employment. A low-dose group (average 32 ppm-yr) and a high-dose group (average 283 ppm-yr) were identified. TWA styrene exposures for the various spraying, rolling, and casting operations ranged from 39-71 ppm (on the average), with exposures during assembly being about 8 ppm. TWA styrene exposure during spraying were sometimes as high as 158 ppm. Blood samples were taken from 36 of the styrene-exposed workers and from 37 age-matched workers (i.e., controls) in the same factory who were not exposed to styrene. Lymphocytes in peripheral blood were cultured and examined for

chromosome aberrations and SCE. The styrene-exposed workers had a significantly higher ($p<0.001$) number of chromosomal aberrations compared with the controls (7.9 vs. 3.2 aberrations/100 cells). There was no significant difference between the average numbers of chromosomal aberrations of the highly exposed and the less exposed styrene workers. There was a significant increase ($p<0.05$) in the average frequency of SCE in cells originating from 20 styrene-exposed workers in comparison with 21 controls (8.4 vs. 7.5 SCE/cell). Again there was no difference between the highly and less exposed groups. Interviews were performed when the blood samples were taken. Multiple regression analysis showed that among 9 factors introduced into the analysis (frequency of chromosomal aberrations, age, duration of employment, exposure to styrene, smoking habits, alcohol consumption, exposure to diagnostic X-rays, other solvents, use of breathing mask), only exposure to styrene showed a high positive correlation to the frequency of chromosomal aberrations [132].

In 1978, Fleig and Thiess [76] and Thiess and Friedheim [75] studied 14 workers employed for 2-24 years in three plants processing unsaturated polyester resins. At the time of the study, styrene concentrations as measured by colorimetric indicator tubes ranged from less than 50 to 300 ppm [75]. Mandelic acid concentrations in urine samples from the workers ranged from 100 to 1,500 mg/l [76]. Five of the 14 workers had increased GGTP (>28 units/ml) [75]. The investigators [76] found a significant excess (level of significance was not given) of chromosomal aberrations in the lymphocytes of peripheral blood from the styrene workers as compared to a control group of 20 workers from the same plant not exposed to styrene (9.2 vs. 5.5%). Fleig and Theiss [76] suggested that the chromosomal changes in these workers were probably due to styrene oxide or other exposures such as methylene chloride, rather than to styrene. Mention was made of a finding that styrene oxide was generated due to the use of peroxides, but data was not given on styrene oxide exposures.

However, there have been studies showing no significant increases in chromosome aberrations among styrene-exposed workers. An investigation of 24 styrene-exposed workers (20 men, 4 women) assigned to laboratory and technical service operations in a German polyester processing plant was reported in 1979 by Theiss and Friedheim [133] and in 1980 by Theiss et al. [134]. Their age range was 23-59 years, and they had been working with styrene for 4-27 years. The average styrene exposure was 6 ppm (range 1-12 ppm) in the laboratory and 58 ppm (range 1-178 ppm) in the technical service operation. Samples were collected with a "Personal Air Sampler" and analyzed with a gas chromatograph. The workers were given thorough clinical examinations that included personal history, chest X-rays, and laboratory studies including body plethysmography, EEGs, ECGs, blood counts, and blood chemistry determinations [133]. Findings were not relatable to styrene exposure, and there were no patterns of disease found. Except for one worker known to imbibe alcohol excessively, the neurological status of all workers was normal. One of the women, a diabetic treated with insulin, had given birth to a stillborn child. Another woman had aborted in the second month of pregnancy. Chromosome analyses of lymphocytes in peripheral blood

were carried out for all 24 workers as well as 24 controls from the same plant. The control group was comprised of medical department and office staff, and plant maintenance workers, none of whom were exposed to radiation or suspected chemicals at the time of testing. Urinary mandelic acid excretion did not exceed 350 mg/g of creatinine in any case; 19 of 22 workers tested had values below 80 mg/g. The investigators [133,134] considered 350 mg mandelic acid/g of creatinine to be a tolerable limit from the standpoint of occupational medicine. The mean frequency of chromosomal aberrations (i.e., chromatid and isochromatid gaps, breaks, fragments, chromatid interchanges, and dicentric chromosomes) was 5.1% in the styrene workers vs. 3.8% in the controls, a non-significant difference as determined by Theiss et al. [134]. However, Norppa et al. [135], in a 1981 discussion of this study [134], considered the results to show an increased frequency of cells with aberrations, when gaps were included.

In 1981, Watanabe et al. [136] examined peripheral blood lymphocytes of 16 workers occupationally exposed to styrene in two facilities (designated as I and II) where TWA styrene exposures were about 70 ppm and 35 ppm, respectively, as determined by carbon felt dosimeters and gas chromatography. Mandelic acid concentrations in the urine collected at the end of the work shift ranged from 90-4,300 mg/l (mean 647 mg/l) at Facility I and 300-1,360 mg/l (mean 526 mg/l) at Facility II. As compared to age- and sex-matched controls, the styrene-exposed workers showed no statistically significant increase in chromosomal aberrations (3.3% in Facility I and 3.6% in Facility II vs. 2.9% in the controls) or SCE frequencies (7.8% in Facility I and 6.7% in Facility II vs. 7.6%).

In 1982, Pero et al. [137] examined lymphocytes from Swedish workers exposed to styrene for genotoxic effects using unscheduled DNA synthesis (UDS) as the indicator of DNA damage. Heparinized blood specimens were taken by venous puncture from 38 male workers in a fibrous glass-reinforced polyester plastics factory where 8-hour TWA styrene exposures, as determined by gas chromatography, were 1-40 ppm. The workers (average age, 38.7 years) had been exposed to styrene for 1-23 years (average, 8.1 years). Twenty workers (average age, 36.2 years) were selected as a control group from a mechanical industry in the same town. Age distributions and smoking habits were similar in both the styrene-exposed and control groups.

Pero et al. [137] examined the possibility that lymphocytes isolated from styrene-exposed workers might have an altered level of unscheduled DNA synthesis (UDS) when the UDS was induced *in vitro* by either N-acetoxy-2-acetylaminofluorene (NA-AAF) or ultraviolet radiation (UV). The mean level of NA-AAF-induced UDS was significantly increased ($p<0.001$) for the styrene-exposed workers when compared to the mean level for the unexposed controls. There was no significant effect on UV-induced UDS from the *in vivo* styrene exposure. These results, in addition to lymphocyte cultures exposed *in vitro* to styrene, indicated to the investigators [137] that styrene exposure did not alter the efficiency of DNA repair synthesis, but rather predisposed lymphocytes to an increased risk for DNA damage from subsequent exposures to genotoxic agents that are dependent on cellular metabolism.

During 1977, Brooks et al. [91] studied 152 styrene-exposed workers (82 women and 70 men) and compared them with 34 female workers with no current styrene exposure. The styrene-exposed workers made reinforced plastic boats. Some of the workers sprayed the styrene-containing resin; others performed hand lay-up or other functions. Workers in the comparison group produced electronic circuit boards and, although they were exposed to many chemicals, their TWA exposures were always much lower than the respective OSHA limits. Table IV-14 contains information that describes the workers from both the study and comparison groups.

TABLE IV-14

DESCRIPTION OF WORKERS FROM STUDY AND COMPARISON GROUPS

Sex	Study Group Female	Study Group Male	Comparison Group All Female
Number	82	70	34
Mean age, years	41	37	38
Age range, years	19-72	18-76	19-56
Smokers	38	36	17
Exsmokers	7	18	1
Nonsmokers	36*	16	16
Average time on present job, months	77	85	62

*One woman did not respond
Taken from Brooks et al. [91]

Information about the workers was obtained from medical histories and physical examinations, psychomotor tests, CBCs, and pulmonary function tests. Additional information included data about the environmental concentrations of styrene and other contaminants from three industrial hygiene studies, and concentrations of mandelic and phenylglyoxylic acids in urine and of styrene in the blood and breath. Brooks et al. [91] combined the environmental data from all three surveys to characterize the styrene exposure for each job category; these data are presented in Table IV-15.

TABLE IV-15

STYRENE CONCENTRATIONS IN THE AIR OF THE STUDY FACTORY

Job Category	Number of Samples	8-hour TWA Styrene Exposure, ppm Mean ± SD
Prefabrication	12	2.8 ± 1.4
Gel coat spraying	6	68.5 ± 59.7
Hand lay-up	63	83.4 ± 42.7
Hand lay-up, other areas	18	25.7 ± 26.2
Woodwork/upholstery	11	3.4 ± 2.1
Final assembly	18	3.2 ± 1.8
Custom molding	18	6.5 ± 3.9
Small boat assembly	4	4.1 ± 1.0
Miscellaneous	2	3.9 ± 3.1

SD = standard deviation
Taken from Brooks et al. [91]

Data in Table IV-15 were obtained from the gas chromatographic analysis of 152 charcoal tube personal samples. In addition to these TWAs, the investigators recorded peak styrene concentrations in the range of 200-800 ppm. These peaks occurred during spraying operations.

To describe styrene absorption and excretion more completely, Brooks et al. [91] determined the concentration of styrene in the workers' blood and expired air. A statistically significant relationship ($r=0.79$, $p<0.001$) between the post-shift concentration of styrene in exhaled air and the styrene concentration of inspired air over the workshift was found. The data indicated that an 8-hour TWA exposure at 50 ppm styrene would result in a post-shift expired breath concentration of about 5.7 µg/liter. There was also an excellent correlation ($r=0.74$, $p<0.001$) between the concentration of styrene in inspired air during a workshift and that in venous blood at the end of a shift.

Brooks et al. [91] found that the styrene concentration in the expired air increased rapidly during the first 2 hours of exposure, remained relatively constant during the shift, then decreased slowly over the next 16 hours. The concentration of styrene in blood, however, rose continuously throughout the exposure period. Styrene concentrations in the blood declined to pre-shift values during the 16 hours following exposure [91].

Because of their hand lay-up work, the 152 workers studied had significant skin contact with the resin mixture [91]. Based on complaints, 41% of the styrene workers had a rash during the past year, and 19% had a rash at the time of the study, both significantly different ($p<0.05$) than the control group. These rashes were on the forearms in 29% of the workers; on the back of the hands in 15%; on the trunk in 14%; and on the upper arms in 12%. In the comparison group, only four workers (12%) reported a rash during the past year and one (3%) at the time of the study. A dermatologist diagnosed the styrene workers' rashes as follows: 18 workers with fibrous glass dermatitis, 6 with contact dermatitis, 7 with nonspecific dermatitis, 10 with acne vulgaris, and 3 workers with other inflammations.

Medical histories revealed a lower incidence of colitis, kidney or bladder infections, and anemia among workers of the study group than in the comparison group. There were no significant differences in the incidence of eye, nose, and throat irritation between the study and the comparison groups, nor were there any significant differences in the incidence of symptoms indicative of cardiovascular or neurological damage, nor were the reproductive histories of the women in the study and comparison group different.

Brooks et al. [91] did find statistically significant differences in the lung function of workers in the study and control groups. Seven workers (4.6%) in the study plant had FVC less than 80%, 7 (4.6%) had FEV_1/FVC X 100 below 70, 13 (8.6%) had FEV_1 less than 80%, and 24 (15.9%) had forced expiratory flow between 25 and 75% of vital capacity (FEF (25-75)), less than 70% of predicted values. No workers in the control plant had abnormal pulmonary function as indicated by FEV_1/FVC, FVC, or FEV_1; one of the subjects (2.9%) in the control group had a FEF (25-75) below 70%. Brooks et al. [91] concluded that since some subjects with abnormal pulmonary function were nonsmokers, the statistical difference between the study and control groups could suggest an occupational origin for the abnormality.

Possible acute effects of styrene exposure were studied by examining pre- and post-shift psychomotor performances of the exposed and comparison groups. The results of the tests for choice reaction time, Flanagan Coordination, Neisser letter search, and digit span were significantly worse for the styrene-exposed group as compared to the control group. However, as noted by the authors [91], a bias may have been introduced since a pre-requisite of employment at the control plant was the passing of a dexterity test. Performance on each test administered showed either no change or slight-to-moderate improvement post-shift in both the styrene-exposed group and the control group when compared to their pre-shift performances. When the styrene-exposed workers were divided into two

groups, one exposed at a mean TWA concentration of about 9 ppm (range, 4-120 ppm) and the other at about 82 ppm (range, 9-244 ppm), no significant difference between the groups was found in terms of effects of styrene on pre- or post-workshift performance of psychomotor tests.

Additional analysis (correcting for workers' ages) by Brooks et al. [91] of the psychomotor data, revealed a significant correlation ($p<0.025$) between decreased performance on the Neisser letter search test and duration of employment for the group with an average TWA styrene exposure of about 82 ppm. For the same group, impaired performance of both the Digit Span test and the Flanagan Coordination test was associated with duration of employment, although it was not statistically significant. Based on these results, Brooks et al. [91] concluded that exposure to styrene at an average concentration of about 82 ppm impaired workers' performance on the Neisser letter search test and, possibly, tests of coordination and memory.

Brooks et al. [91] also determined the concentrations of mandelic and phenylglyoxylic acids in the urine of the styrene-exposed workers. When the log of the sum of the mandelic acid and phenylglyoxylic acid concentrations in post-shift urine was plotted against the log of the TWA styrene concentration for that shift, the correlation coefficient r was 0.925 ($p<0.00001$); when only the concentration of mandelic acid was used, the correlation coefficient was 0.93 ($p<0.00001$). There were also excellent correlations between the log of the post-shift urinary mandelic acid concentration and the log of the post-shift venous blood styrene concentration ($r=0.899$, $p<0.001$) and the log of the styrene concentration in post-shift expired breath ($r=0.877$, $p<0.001$).

In 1979, Kjellberg et al. [392] studied 7 boat-fabrication shop workers and compared them with 7 workers in a mechanical industry in the same Swedish town. The boat workers were exposed to styrene while making the boats and to acetone during the cleaning of equipment. TWA exposures were found to be 3-14 ppm of styrene and 8-60 ppm of acetone. Of the behavioral tests applied, namely, reaction time, Bourdon-Wiersman, and reaction time additions, only the reaction time test showed a significant difference ($p<0.05$) between the RP/C workers and the comparison group. This reaction time test involved measurement of the time between the illumination of a lamp and the press of a button by the subject. Kjellberg et al. [392] concluded that work exposure had caused the decreased reaction times, but were unable to determine whether styrene, acetone, or their combined effect was responsible.

In a 1980 study of 27 British men engaged in boat building, Cherry et al. [138] found effects attributable to CNS depression. The styrene-exposed workers were compared to a control group of workers from the same plant, with no styrene exposures, of almost the same average age (23 years in exposed workers vs. 26 years in referents). Personal TWA exposures averaged 117 ppm styrene in the morning and 52 ppm in the afternoon, for an overall average of 92 ppm. Blood styrene averaged 6.9 μmol/liter in the exposed and 0.6 μmol/liter in the control workers; urinary mandelic acid

averaged 581 μmol/mmol creatinine in the styrene-exposed workers, with no value being given for controls. Changes in mood were reported in both groups, but more so in those workers exposed to styrene; changes in mood were correlated with blood styrene concentrations. The reaction times of styrene-exposed workers were slower than the referents in the morning, but their reaction time increased during the day so that in the afternoon they were similar to those of referents. The styrene-exposed workers also fared worse in other behavioral tests than did the controls, but the differences were minor. The styrene-exposed workers reported being more fatigued than did the men in the comparison group, and they also reported being more tired on Friday evening than on Monday evening.

In 1980, Hemminki et al. [139], described finding a greater number of spontaneous abortions among female chemical workers than would be expected from the rate among all Finnish women, with part of this excess occurring among styrene workers. The investigators [139] obtained information on 9,000 female workers during the period 1973-1976 from union and national Registry files, and found that 52 of the women had reported spontaneous abortions. The national Registry was based on general hospital inpatients, not including aborting women not treated, women treated on an outpatient basis, or women treated in private hospitals, which provided only about 2.2% of the obstetrics-gynecology beds in Finland. Abortion rates were expressed as the ratio of spontaneous abortions to pregnancies (SA/P) and as the ratio of spontaneous abortions to births (SA/B). Hemminki et al. [139] used both ratios because they believed the former index underestimated the risk, inasmuch as some induced abortions included in total pregnancies would have miscarried, and the latter index overestimated the risk because induced abortions were not included; there is a high rate of induced abortions in Finland. The results of the study are shown in Table IV-16.

TABLE IV-16

SPONTANEOUS ABORTIONS OF
FINNISH CHEMICAL WORKERS IN 1973-1976

Branch of Employment	Number of Spontaneous Abortions (SA)	SA x 100 / Pregnancies (SA/P)	SA x 100 / Births (SA/B)
All women in Finland	15,482	5.52	7.98
Union of Chemical Workers	52	8.54**	15.57***
Plastics Industry	21	8.94*	17.80***
Styrene Production and Use	6	15.00**	31.59***
Viscose Rayon Industry	9	11.25*	22.50***
Laundries	7	10.14	16.67*
Pharmaceutical Industry	5	10.20	22.72*

*significant difference from "All women in Finland," $p<0.05$
**significant difference from "All women in Finland," $p<0.01$
***significant difference from "All women in Finland," $p<0.001$
Taken from Hemminki et al. [139]

There were statistically significant excesses in spontaneous abortions among members of the Union of Chemical Workers and among several subgroups. There was a significant excess among plastics workers, especially among styrene and viscose rayon workers. There were also excesses, significant only in terms of the SA/B index, among workers in laundries and in the pharmaceutical industry. There were 6 spontaneous abortions among styrene workers, resulting in an SA/P index of 15.00 ($p<0.01$) and an SA/B index of 31.59 ($p<0.001$), the highest indices of any group tabulated in the report [139], compared to 5.52 and 7.98, respectively, in the overall Finnish population. Hemminki et al. [139] stated that the styrene workplaces included mainly reinforced plastics workshops.

In 1982, Harkonen and Holmberg [140] studied 67 female lamination workers occupationally exposed to styrene to evaluate the possible embryotoxic effects of styrene. The average age of the workers at the 6 Finnish factories manufacturing reinforced plastics was 30 and ranged from 19-40 years. The duration of past styrene exposure was 0.5 to 10 years, and averaged 4.5 years. No styrene measurements were made in this study, but the investigators [140] stated that in a previous study in the Finnish polyester plastics industry, the median TWA exposure to styrene in lamination work was 66 ppm. Each of the laminators was matched by age with textile or food production workers of a similar social class with no occupational solvent exposures. A questionnaire was personnally administered by the same interviewer during 1979-1980. The obstetric

histories of the subjects (laminators) were divided according to the time prior to styrene exposure and the period of styrene exposure. The obstetric histories of the controls were likewise divided to correspond to the time periods of their age-matched exposed subjects. Table IV-17 presents data on pregnancies, births, spontaneous abortions, and induced abortions.

TABLE IV-17

NUMBER OF PREGNANCIES, BIRTHS, SPONTANEOUS ABORTIONS, AND INDUCED ABORTIONS AMONG 67 LAMINATION WORKERS AND MATCHED CONTROLS

	Before Styrene Exposure		During Styrene Exposure	
	Laminators	Controls	Laminators	Controls
Pregnancies	48 (84)	48 (80)	12 (16)	20 (22)
Births	40 (69)	39 (67)	3 (4)*	14 (14)
Spontaneous abortions	8 (8)	5 (8)	3 (4)	4 (4)
Induced abortions	6 (7)	5 (5)	8 (8)	4 (4)

Note: The number of occurrences is given in parentheses.
*different from controls, $p<0.01$
Taken from Harkonen and Holmberg [140].

Prior to the period of styrene exposure, the number of women with pregnancies, births, spontaneous abortions, and induced abortions (or the number of occurrences of each) did not differ significantly for the styrene-exposed and control groups. During styrene exposure, the number of pregnancies was not significantly different but the number of births among the exposed subjects was significantly less than the controls (4 vs. 14, $p<0.01$). One cause leading to this difference was the higher number of induced abortions (8 vs. 4); this difference, however, was not significant. There were two birth defects reported by both the laminators and the controls. The two groups did not differ in the use of contraceptives or drugs, but smoking and the consumption of alcohol during pregnancy were more common in the styrene-exposed group [140].

To summarize this subsection, these studies of workers in factories where styrene copolymers (mainly RP/C) were produced have demonstrated effects that have been attributed to styrene exposure despite potential exposure of the workers to other chemicals. It is likely that some of the reported effects on worker health such as eye and respiratory tract irritation, dizziness, headache, nausea, and feelings of intoxication were due to styrene exposures at peak concentrations. Some other effects such as

abnormal EEG patterns, increased incidence of chromosomal aberrations and sister chromatid exchanges, increased incidence of spontaneous abortions, visuomotor inaccuracy, and impaired psychomotor performance have also been reported.

Epidemiological Studies

A retrospective cohort mortality study of the German styrene and polystyrene production plant previously described in the Clinical Studies Section [75,76,77], was reported in 1978 by Frentzel-Beyme et al. [78]. Airborne styrene concentrations in production areas were about 1 ppm in 1975 [75]. In the mortality study, records of 1,960 past and present workers were reviewed; causes of death as listed on death certificates of 74 workers that died during 1956-1976 were compared with age-specific mortality of the population of the whole country. The proportion of deaths due to liver and digestive organ disease was higher in the styrene-exposed workers than in the overall population of the country. However, the investigators [78] did not identify their criteria of diagnosis of liver and digestive organ diseases. Frentzel-Beyme et al. [78] suggested that the higher incidence of liver disease might be because these workers were from the primary wine-producing region of the country, implying a greater than average alcohol consumption. However, no data on the alcohol consumption of either the styrene-exposed or unexposed groups were given. A total of 12 deaths from cancer were recorded among the styrene workers (3 lung, 2 stomach, 2 pancreas, 2 colon, 1 rectum, 1 spleen, and 1 probable kidney cancer). The incidence of these tumors did not differ from that of the overall population of the country. The proportion of deaths due to cardiovascular diseases was also less than in the country as a whole.

In 1974, Maier et al. [84] reported the results of a proportional mortality study of a U.S. styrene and polystyrene plant previously described in the Clinical Studies Section [58,81,82,83,84,85,86,87]. Production of styrene and butadiene monomers began at this plant in 1943, with butadiene produced until about 1950; since 1950, the principal product had been polystyrene [82]. Prior to 1962, benzene was used as a raw material in the on-site production of ethylbenzene; subsequently, ethylbenzene for styrene monomer production had been shipped into the plant [141]. In a 1973 industrial hygiene survey, Maier et al. [84] determined that exposures to styrene, benzene, ethylbenzene, or toluene were each usually less than 10 ppm. Death certificates for 46 workers from this plant who had died during the previous 5 years were analyzed by Maier et al. [84] by a comparison to the mortality of males, aged 60-64 years, in the nation as a whole. Of the 46 deaths, 1 was a suicide and 4 were accidents. Grouping the remaining 41 death certificates into either "Coronary Disease," "All Forms of Cancer," "Cerebral Vascular Disease," "Respiratory Disease," "Diseases of the Digestive System," or "All Other" revealed no significant differences from the expected proportion of deaths in any classification. Due to the small number of deaths involved, as well as the use of mortality rates from males aged 60-64 years for comparison, this study is difficult to interpret.

However, these findings were verified by a more extensive mortality study reported in 1978 by Nicholson et al. [83]. The vital status in 1975 of 560 men who were working in this factory on May 1, 1960 and who had been employed at least 5 years was determined. The investigators [83] expected about 106 deaths but 83 were found. Deaths from "Heart and Circulatory Diseases," "Respiratory Diseases," "Cancer," and "Other Causes" categories were not greater than expected. Because of potential benzene exposures, special attention was given to leukemia as a cause of death. Two cases of leukemia and one lymphoma were recorded on the 83 death certificates. Death certificates provided by the company of 361 other workers who had been employed at this factory for 6 months or more were examined, and five additional cases of leukemia and four additional cases involving the lymph system were recorded on these. Although the information available from the 361 randomly collected death certificates was "suggestive" of an excess risk of death from leukemia or lymphoma in this factory, Nicholson et al. [83] concluded that the data was not definitive.

In 1980, Ott et al. [31] studied the mortality rate of workers at four different locations of a U.S. manufacturer of styrene and styrene products. Work activities were mainly in styrene production, polystyrene production, copolymerization of styrene with butadiene or acrylonitrile, color mixing, resin extrusion, and in support activities such as research, pilot plant development, and product development. Based on surveys conducted between 1962 and 1975, estimated TWA styrene exposures were all below 10 ppm, including one survey in which there were excursions to 50 ppm. In some units, there were exposures to benzene which were estimated to have been below 15 ppm during the period 1953-1972, but much higher earlier. There were other exposures recorded, such as ethylbenzene (less than 10 ppm), ammonia (about 15 ppm), acrylonitrile (less than 10 ppm), vinylidene chloride (less than 1 ppm), formaldehyde (about 3 ppm), cleaning solvents, and various pigments and dyes.

The earliest operation was 40 years old, but how many, if any, workers had worked with styrene that long was not stated; however, 2,904 workers had been employed for at least 1 year in styrene operations. Of the total cohort, 2,360 workers (81%) were from the company's Michigan location, with the remaining workers from plants in Texas, Connecticut, and California. Verification of vital status was completed for all but 88 former workers [31].

During the period 1940-1975, there were 303 deaths found among styrene workers (professional and nonprofessional research workers, supervisors, and production workers), compared with 425 expected in the U.S. white male population; this total of 303 did not include 17 deaths among 164 former workers exposed to arsenic, asbestos, or high levels of vinyl chloride. There were 58 deaths from the "All Malignant Neoplasms" category compared with 76.5 expected. Except as discussed below, the number of deaths from specific causes did not exceed the expected number. There was a slight excess of deaths from the category "Bronchitis, Emphysema, and Asthma" (10 observed vs. 7.5 expected), "Malignant Neoplasms of the Lymphatic and

Hematopoietic Tissue except Leukemia" (7 observed vs. 5.3 expected), and "Leukemia" (6 observed vs. 3.4 expected). In addition to the 13 cases in which leukemia or lymphoma (malignant neoplasms of the blood forming organs) were reported as the cause of death, there were 2 cases where the presence of leukemia or lymphoma was mentioned on the death certificate but where another cause of death was listed, and 6 cases identified as still living. The incidence of lymphocytic leukemia cases were significantly greater ($p<0.05$) than expected on the basis of age-specific incidence rates from the Third National Cancer Survey (7 observed vs. 1.6 expected). Of these cases, 5 cases (1 of whom was still living) vs. 0.26 cases expected ($p<0.05$) occurred in workers in operations involving colorant blending and roll compounding or extrusion of plastics, areas where polymer dusts, solvents, colorants, and extrusion fumes composed of vapors including styrene and ethylbenzene were present [31].

The production and nonprofessional research workers (2,310 men) were also studied separately. There were 282 deaths in this group vs. 357.8 expected from U.S. white male data and 287.6 expected from data published in 1954 on workers from the company's Michigan location. (There was an overlap between the two cohorts as 1,333 of the 8,171 workers from the 1954 comparison group were included in the later study group.) Of the 282 deaths, 55 were due to "Malignant Neoplasms," vs. 64.2 expected in the U.S. population and 65 in the 1954 company comparison group. There were 6 deaths from "Leukemia," a significant difference ($p<0.05$) from the 1.6 expected in the company comparison group but not from the 2.9 expected in the U.S. population [31].

In summary, mortality was less than that of the corresponding white male population. Deaths due to malignant neoplasms were fewer than expected, but an increase in lymphatic leukemia was observed among a subgroup of workers who had exposures to polymer extrusion fumes (including styrene), solvents, and colorants. However, the etiology of the lymphatic leukemia could not be established by Ott et al. [31].

In 1978, Ahlmark [142] described the cancer incidence and mortality among a group of workers in Sweden who were exposed to styrene in the manufacture of reinforced plastics. This was a retrospective cohort study in which entry into the cohort was defined by the date of first employment. From as many reinforced plastics companies as could be located and as were willing to participate, persons working with styrene up to the year 1970 were identified. Sufficient information to use in the study was found on 1,114 men and 91 women. Exposure information for these workers was not provided, but Ahlmark [142] estimated, from information on reinforced plastics operations in Sweden, that mean styrene exposures were 250-300 ppm in the late 1960s and early 1970s and were probably higher earlier. The 1,114 men ranged in age from the late teens to the 70's and the 91 women from the 20's to the 60's. Twelve deaths from cancer were found in the study population from the Social Welfare Board Cancer Register for 1959-1976 and the Central Statistical Bureau Mortality Register for 1972-1976, which were less than the 16.6 expected [142].

While no excess of cancer was found in this group of workers, exposed to styrene at concentrations estimated to have been 250-300 ppm and higher, Ahlmark [142] pointed out that latency periods for many of these workers were not great, so, if styrene were a carcinogen, more cases would be expected later. The problem of varying latency was handled in the calculations by computing person-years of employment in each age category in the study cohort. However, only 472 workers (39%) in the cohort had a latency period of 11 years or more, so, although not given, the number of workers with more more than 20 years since first exposure was probably small.

Uptake, Metabolism, and Elimination

Studies were reported by Bardodej et al. [143] in 1961 and Bardodej [144] in 1964 on the uptake, metabolism, and elimination of inhaled styrene by humans. These investigations were later summarized in 1966 and 1970 by Bardodej and Bardodejova [100,145]. Human volunteers, with no history of occupational styrene exposure, were experimentally exposed to styrene in a closed chamber with no provisions for changing chamber air. To study styrene absorption, Bardodej [144] measured each subject's minute volume during exposures to styrene at 21, 49, 106, and 188 ppm. The range of minute volumes was 6-40 liters. Styrene vapor concentrations inside the chamber and in the breath were monitored by ultraviolet spectrophotometry. The percentages of styrene retained by the lungs were calculated from styrene concentrations in the inhaled and the exhaled air. Over the range of styrene concentrations studied, the subjects retained about 60% of the inhaled styrene regardless of minute volumes or duration of exposure. When the subjects were removed from the test atmosphere, styrene concentrations in exhaled air decreased within seconds to less than half the levels found immediately after removal from exposure.

To study styrene metabolism, urine was collected from subjects exposed at 22, 129, and 235 ppm for 8 hours and analyzed for styrene and its metabolites. Styrene concentrations were below the detection limit of the photometric method used. Urine samples were subjected to paper chromatography, using several liquid phases and reagents for detection of mandelic, styrene thiolic, hippuric, and phenylglyoxylic acids, phenylglycol, phenylglycol glucuronide, and omega-hydroxyacetophenone [144]. The presence of phenylglycol, the glucuronide of phenylglycol, omega-hydroxyacetophenone, and styrene thiolic acid could not be demonstrated in the urine of exposed subjects, nor could an increase in hippuric acid concentration [143]. Styrene oxide could not be found in the urine samples by using a spectrophotometric method. Both mandelic and phenylglyoxylic acids were found and confirmed.

Urinary mandelic and phenylglyoxylic acids accounted for 85% and 10% of the absorbed styrene, respectively. Eighty percent of orally administered mandelic acid was excreted as such, with 15 percent excreted in the urine as phenylglyoxylic acid [144]. Concentrations of urinary mandelic acid of subjects at the end of 8-hour exposures to styrene at 22, 129, and 235 ppm

averaged about 500, 1,350, and 2,700 mg/l, respectively [143,144]. After an 8-hour exposure to 22 ppm, urinary mandelic acid, expressed as the ratio of mandelic acid to creatinine, was maximal at the end of exposure (i.e., 0.4) and declined linearly over the next 20 hours to about 0.06.

In 1965, Fiserova-Bergerova and Teisinger [146] reported the retention of styrene in subjects exposed at 24 ppm. Ultraviolet and polarographic methods (which they found equivalent) were used to analyze for styrene in inhaled and exhaled air during 2- and 5-hour exposures. In all experiments, the subjects exhaled through the mouth; they inhaled through the nose in some experiments and through the mouth in others. The average styrene retention from the very beginning of exposure was 66% following nasal inspiration and 59% after oral inspiration, and did not change during the 2 or 5 hours of exposure. In the analysis of a single deep breath, alveolar styrene concentrations were found to be about 6.2% of the inhaled concentration; after an expiration pause (30 seconds), alveolar concentrations were about 5.5%. This indicated that transfer of styrene from the blood to the lungs was minor. No styrene was found in exhaled air one minute after removal from exposure [146].

Studies of pulmonary absorption and the elimination of styrene inhaled at 70, 103, 115, 200, and 206 ppm for 4 or 8 hours were reported by Fernandez and Caperos [147] in 1977 and Caperos et al. [148] in 1979. Pulmonary ventilation, respiratory rate, and alveolar concentrations of styrene were monitored frequently during the exposures. Removal of styrene from inhaled air by blood was practically constant throughout all of the exposures. The amount of styrene absorbed ranged from 90.5% during exposure at 70 ppm for 4 hours to 86.8% during exposure at 206 ppm for 8 hours. The styrene analytical method (gas chromatography) under their sampling conditions had a lower limit of detection of 0.01 ppm in 25 ml of expired air. Some styrene was found in alveolar air for about a week after the exposures. The calculated total amount of styrene eliminated by the lungs accounted for 2.6% (1.5-4.4%) of that absorbed, independent of exposure conditions [147]. On the average 54% was excreted in the urine as mandelic acid and 38% as phenylglyoxylic acid. Half of the urinary mandelic acid and one quarter of the phenylglyoxylic acid formed was excreted during the 8-hour exposure to 103 or 206 ppm styrene with the rest being excreted within 3-5 days [148].

After administering styrene at 50 and 150 ppm through a mouthpiece, Astrand et al. [88] in 1974 measured its concentrations in the alveolar air and arterial and venous blood of human volunteers. These measurements, along with routine cardiac and respiratory tests, were conducted on 2-14 male subjects who were 21-28 years old. Measurements were made at rest and after exercise on a bicycle ergometer at 50, 100, and 150 Watts (W) to study the effects of various workloads on styrene uptake. Mixtures of air that contained 4% carbon dioxide and various amounts of styrene were used to observe the effects of increased respiration on styrene metabolism without the complicating effects of an increased cardiac rate. The styrene concentrations found in the alveolar air and in the arterial and venous blood under different conditions of exposure are presented in Table IV-18.

TABLE IV-18

AVERAGE STYRENE CONCENTRATIONS IN ALVEOLAR AIR AND BLOOD OF SUBJECTS EXPOSED TO STYRENE AT 50 AND 150 ppm

Exposure Conditions				Styrene Concentration (ppm)		
Styrene (ppm)	Workload (W)	CO2	N*	Alveolar Air	Arterial Blood	Venous Blood
50	0	No	6	8.8	0.5	0.3
50	50	No	6	9.5	1.9	1.4
150	0	No	14	23.0	1.8	1.0
150	0	Yes	2	26.3	5.3	2.4
150	50	No	11	29.9	6.5	4.7
150	50	Yes	2	28.8	12.3	7.7
150	100	No	4	32.5	11.6	7.9
150	150	No	4	35.4	15.9	12.4

*Number of subjects
Taken from Astrand et al. [88]

Pulmonary ventilation, heart rate, and oxygen uptake were unaffected by exposure to styrene. Alveolar styrene concentrations rose only slightly while the arterial concentrations almost tripled in response to a 50-Watt workload. The alveolar styrene concentration reached a plateau after only 1 minute of exposure, but the arterial styrene concentration increased during the entirety of each 30-minute exposure period. Further increases in the arterial styrene concentrations also occurred after exposure to styrene in air containing 4% carbon dioxide [88].

Because of the poor relationship between alveolar and arterial styrene concentrations, Astrand et al. [88] concluded that alveolar air was a poor indicator of the extent of exposure to styrene vapor. Astrand et al. [88] recommended that a fingertip blood sample be used to evaluate styrene uptake because styrene concentrations in arterial and capillary blood were in very good agreement. Urinary mandelic acid was determined colorimetrically before exposure and at 3-hour intervals for 24 hours after removal from exposure. The mandelic acid concentrations peaked 3-5 hours after exposure and fell to pre-exposure values 9-13 hours after concluding exposure. In one experiment, the concentrations of styrene in inspired and expired air were continuously measured in two individuals at rest during four consecutive 30-minute styrene exposures at 50, 150, 250, and 350 ppm. More than two-thirds of the styrene inhaled during each 30-minute period was retained by the subjects. The amount of styrene absorbed was 750 mg during this

sequential 2-hour exposure that averaged 200 ppm of styrene, and it was determined that about 50% of the amount absorbed was excreted as mandelic acid. Because a nonspecific method was used for determining mandelic acid, it is likely that not all of the mandelic acid excreted was measured. Astrand et al. [88] concluded that measurement of urinary mandelic acid would not provide an accurate indication of styrene exposure because there was a large variation between subjects at low exposures. However, with the nonspecific method used to determine mandelic acid, background values were large and variable; consequently, slight differences in mandelic acid concentrations might not have been detectable.

Hake et al. [70] in an inhalation study summarized earlier in the Experimental Exposures Section, concluded that blood analysis, metabolite to creatinine ratio in 24-hour urine samples, and alveolar breath analysis 15 minutes after exposure were all useful indicators of styrene exposure, but they preferred breath analysis provided analysis could be performed the same day as exposure occurred. Such a sample taken 15 minutes after exposure and containing more than 2.8 ppm styrene indicated to the investigators [70] a styrene burden injurious to health; this was associated with changes in EEGs, visual evoked response, and pulmonary function, and in the onset of such symptoms as headache, dizziness, and irritation of the eyes and upper respiratory tract. The experimental exposures resulting in styrene concentrations of 2.8 ppm in alveolar air (15 minutes after exposure) were 100 and 125 ppm. No subject exposed at 20 ppm had more than 0.8 ppm styrene in his alveolar breath 15 minutes after exposure.

Gotell et al. [35], in field studies of RP/C production workers summarized earlier in the Clinical Studies Section, collected breath samples 15 minutes, 2 hours, and 5 hours after the end of the workday and analyzed them for styrene by gas chromatography using a flame ionization detector. The workers were divided into three groups based on TWA exposures to styrene: (I) 235-292 ppm, (II) 89-139 ppm, and (III) 17-32 ppm. When the concentrations of styrene in expired air were plotted against the time after exposure, there was a characteristic rate of styrene excretion for each group based on the level of exposure. Five hours after exposure, the concentration of styrene in expired air was about 0.9 ppm for group I, 0.3 ppm for group II, and 0.2 ppm for group III [35].

Urine samples were collected immediately after work for measurement of mandelic and phenylglyoxylic acids by the methods of Ohtsuji and Ikeda [121] with the results adjusted to a urine specific gravity of 1.024. Control values in 27 nonexposed men were: mandelic acid, 78-434 mg/l; and phenylglyoxylic acid, 20-196 mg/l [35]. The overall linear correlation coefficients (Groups I, II, and III) with 8-hour TWA styrene exposure concentrations were 0.75 for mandelic acid and 0.36 for phenylglyoxylic acid. However, the respective correlation coefficients for workers exposed at 8-hour TWA concentrations ranging from 17-139 ppm (Groups I and II) were 0.96 and 0.85, while for the workers in Group III exposed at higher concentrations (i.e., 235-292 ppm), the correlation coefficients were -0.93 and -0.95. These negative correlation coefficients found at the higher

styrene concentrations may reflect an asymptotic curve rather than a real reduction in mandelic or phenylglyoxylic acid concentration. Gotell et al. [35] plotted three linear regression lines to explain the relationship between concentrations of metabolites and airborne styrene. Visual inspection of these plots suggests that the data might best be fitted by a hyperbola. If so, the negative regression would be better expressed as the upper end of such a curve. If these data are indeed properly described by a hyperbola, it appears that excretion of these metabolites approaches a maximum (asymptotically) with increasing dose of absorbed styrene. Whether the limitation is metabolic or excretory is not established, though metabolic limitation seems a more likely explanation.

In 1978, Engstrom et al. [149] found styrene in subcutaneous adipose tissue in volunteer subjects exposed to styrene vapor. Seven male subjects, 22 to 30 years of age, were exposed for two hours to 50 ppm of styrene through a breathing valve and mouthpiece with 30 minutes of rest and three 30-minute work periods on a bicycle ergometer at intensities of 50, 100, and 150 Watts. Average styrene uptake was 490 mg, corresponding to 63% of the amount inspired. Styrene uptake was 5-6 times higher during heavy work than at rest. The average total amount of styrene expired during the 19 hours following exposure was about 3% of the amount retained during exposure.

Needle biopsy of subcutaneous adipose tissue was performed on all of the subjects before exposure and 0.5, 2, 4, and 20-24 hours after the exposure. In addition, four of the men were subjected to biopsies during the 1-2 weeks following exposure. Styrene concentrations in the adipose tissue of the subjects were determined after evaporation of the solvent at 150°C into nitrogen which was continuously exchanged. The gas was collected in 30-ml glass syringes and assayed with gas chromatography. About 24 hours after exposure the average concentration of styrene in adipose tissue was about the same level as 2-4 hours after exposure, i.e., about 3.5 mg/kg. Retention of styrene was noticed as late as 13 days after the 2-hour exposure. The investigators [149] estimated the half-life of styrene in adipose tissue to be 2-4 days.

Also in 1978, Engstrom et al. [150] conducted a similar investigation of three males occupationally exposed to styrene during the processing of polyester tanks. The TWA exposures of the workers were 8, 15, and 20 ppm. The average daily uptake of styrene was estimated to be 193-558 mg. On Monday morning styrene concentrations in adipose tissue were 2.8-8.1 mg/kg and on Friday afternoon were 4.7-11.6 mg/kg. The concentrations were higher in the two workers with the higher exposures (i.e., 15 and 20 ppm) of longer duration (several years) as compared to styrene adipose tissue concentrations in the other worker who had been employed only 2 weeks with an exposure of 8 ppm . Both of the workers with several years of exposure to styrene had a considerable amount of body fat (27 and 41 kg, respectively) as estimated by an anthropometric method. The half-lives of styrene in adipose tissue for these two workers were calculated by Engstrom et al. [150] to be 5.2 and 2.8 days, respectively.

The percutaneous absorption of undiluted and aqueous solutions of styrene was studied in 1968-1969 by Dutkiewicz and Tyras [151,152,153]. With undiluted styrene, either 0.1 ml (88.8 mg) or 0.2 ml (176.8 mg) was applied to the forearms of each of seven subjects. A watch glass was pressed tightly to the skin, and the amount of styrene absorbed was calculated from the difference between the amount applied and the amount recovered after 8-15 minutes. Styrene that was removed from the skin with gauze and from the gauze and watch glass with glacial acetic acid was analyzed colorimetrically. On the average, styrene was in contact with 17.3 sq cm of skin for 11.1 minutes, and 39.4 mg of styrene was absorbed. The average calculated rate of absorption in the seven subjects was 11.9 mg/sq cm/h [151].

In the study of styrene diluted with water, the difference in the concentration of the solution before and after immersing one hand for an hour was directly determined with an ultraviolet spectrophotometer. Evaporation of the solution was prevented by enclosing the beaker and hand in a polyethylene bag. With styrene concentrations of 67.5-264.0 mg/l of water, 14 observations were made on 6 subjects. The rates of styrene absorption increased linearly with styrene concentration. Rates of 38-184 µg/sq cm/h were estimated [151].

Dutkiewicz and Tyras [151] also evaluated urinary mandelic acid and styrene in exhaled breath in the study of percutaneous absorption of styrene. Four subjects each immersed both hands in aqueous styrene solutions (215-220 mg styrene/liter of water) for 2 hours. During the ensuing 24 hours, mandelic acid was determined polarographically after conversion to benzaldehyde. The rate of excretion of mandelic acid in urine decreased exponentially from 3-4 mg/h initially to about 0.7 mg/h at 18-24 hours. On the average, the subjects excreted about 40 mg of mandelic acid in 24 hours or only about 13% of the estimated average amount of styrene absorbed. Traces of styrene were detected in expired air of subjects who had absorbed about 200 mg of styrene. The investigators [151] concluded that contact of both hands with undiluted styrene for 1.5 minutes or with saturated aqueous solutions for 1 hour could result in absorption of styrene equivalent to that absorbed by a worker exposed to airborne styrene at 12 ppm for 8 hours. Whether data from absorption of styrene through the hands can be quantitatively applied to other skin areas is not clear, but at least the data [151] clearly demonstrate that styrene can penetrate human skin.

In 1978, Riihimaki and Pfaffli [154] described the percutaneous absorption of airborne styrene in two male subjects. These subjects were exposed to styrene vapor at a concentration of 600 ppm for 3.5 hours. Each wore socks, pajamas made of a thin cloth, and, to prevent absorption through the lungs, a full-facepiece positive pressure respirator that was monitored for proper operation. They exercised at 100 Watts for 10 minutes of each hour on a bicycle ergometer, and at all other times remained sedentary; this exercise made them perspire for about 15 minutes. Based on amounts of urinary metabolites (mandelic, phenylglyoxylic, and methylhippuric acids) and styrene in expired air, the amount of styrene absorbed through the skin

during the exposure averaged 576.1 μmoles for the two subjects. This amount was estimated to be 19% of the amount that would have been absorbed through the lungs at the same concentrations, assuming a 60% retention rate for styrene at 600 ppm. This amount was twice that absorbed by the lungs during the exposures of three subjects at 10 ppm (576.1 vs. 288.1 μmoles). The small number of subjects and the variability in the data preclude definite conclusions from this experiment, other than to infer that styrene vapor can penetrate intact skin, albeit inefficiently. A question should also be raised about the degree of reliance to be placed on respirators by those working in high concentrations, such as some work in enclosed spaces.

In 1980, Brooks et al. [155] designed a study to determine whether styrene absorption through the skin results in measurable changes in biological indicators of styrene exposure. Eight female workers engaged in hand lay-up operations in fibrous glass boat production during which extensive styrene skin contact occurred were studied. Measurements of expired breath and blood styrene levels and urinary levels of mandelic and phenylglyoxylic acids were made during 4 consecutive days using different experimental conditions including either (1) gloves and protective clothing alone, (2) respirator alone, (3) gloves, protective clothing, and respirator, or (4) no respirator, gloves, or protective clothing. TWA airborne styrene levels ranged from 71-91 ppm, as determined with charcoal tubes and gas chromatographic analysis. Levels of styrene in venous blood and expired breath and excretion of urinary mandelic and phenylglyoxylic acids were no different when gloves and protective clothing were used as protection compared to when no gloves, protective clothing, or respirators were used. Significant reduction in all biological indices studied occurred when respiratory protection was used. Brooks et al. [155] concluded that percutaneous absorption of styrene was not a significant exposure source and did not significantly contribute to the body burden of styrene in the RP/C workers studied who were engaged in hand lay-up operations. The lack of apparent skin absorption was attributed to possible differences in transport phenomena attendant to the use of polyester resins in combination with styrene, which might have inhibited percutaneous absorption [155]. However, Dutkiewicz and Tyras [151] as previously discussed, determined that only 13% of the styrene absorbed percutaneously with hands immersed in an aqueous solution was eliminated as mandelic acid.

In 1978, Guillemin and Bauer [156] reported a study of the excretion of urinary mandelic and phenylglyoxylic acids after experimental exposures to styrene. Nine healthy male volunteers, 21-34 years old, with normal heights, weights, and vital capacities and with no current styrene exposure were used, some several times. The study was conducted in an experimental chamber that had been previously described by Guillemin [157]. It had an internal volume of 10 cu m, and there were provisions for controlling the temperature (22°C) and humidity (50%) and for exchanging the air. Styrene concentrations inside the chamber were monitored continuously with a total hydrocarbon analyzer and periodically by gas chromatography. The experimental parameters are shown in Table IV-19.

TABLE IV-19

STYRENE EXPOSURE SCHEDULE OF HUMAN VOLUNTEERS

Number of Subjects	Number of Exposures	Duration of Exposure (h)	Concentration (ppm)
5	4	4	99-122
4	1	4	200
4	2	8	42-49
9	3	8	100-112
3	2	3.5	99-101

Taken from Guillemin and Bauer [156]

All urine specimens were collected during exposures and for up to 4 days afterwards; urinary mandelic and phenylglyoxylic acids were determined gas chromatographically. The urine samples were divided into two portions with one being analyzed directly for mandelic acid. Phenylglyoxylic acid in the second portion was found indirectly after it was converted to the trimethyl silyl derivative of mandelic acid as described by Guillemin and Bauer [158] and total mandelic acid representing initial mandelic acid and phenylglyoxylic acid was determined. Both mandelic and phenylglyoxylic acids were found in the urine of subjects within an hour of the beginning of styrene exposure [156]. After the 8-hour exposure at 100-112 ppm, the urinary mandelic acid concentration decreased from 1,000 mg/g of creatinine at the end of exposure to about 10 mg/g of creatinine 56 hours later. Urinary excretion of phenylglyoxylic acid decreased exponentially during the 48 hours after exposure.

Urinary mandelic and phenylglyoxylic acid excretion data obtained from individuals exposed to styrene for 8 hours at 50 ppm were indistinguishable from those obtained from individuals exposed for 4 hours at 115 ppm. Thus, these investigators [156] showed that urinary mandelic acid concentrations reflect exposure dose (as estimated by the product of exposure concentration and duration) rather than exposure concentration. Ratios of mandelic acid to creatinine calculated for urine samples collected at the end of exposure and 14 hours later, and total mandelic acid in all urine collected over a 4-day period after exposure were correlated to the exposure dose in terms of ppm times hours of exposure with coefficients of 0.706, 0.668, and 0.873, respectively. The data demonstrated that there is no advantage to measuring phenylglyoxylic acid or mandelic plus phenylglyoxylic acids over measuring mandelic acid only.

In 1974, Ideda et al. [159] measured urinary metabolites of styrene in six workers who were exposed to styrene during the production of electric motor parts in a Japanese factory. On the day the workers were studied, they were exposed at 50-200 ppm for two 80-minute periods with a 200-minute nonexposure interval. One week later, five of these same workers and an additional worker were studied. The workers were exposed that day to styrene at 4-60 ppm for 120 minutes. Styrene concentrations in the workplace were determined by colorimetric detector tubes and by gas-liquid chromatography.

Urinary hippuric acid concentrations following the first exposure (50-200 ppm) reached a maximum a few hours after urinary excretion of mandelic and phenylglyoxylic acids had returned to normal. At the lower level of exposure (i.e., 4-60 ppm) a week later, no increase in hippuric acid above control values could be detected. The reason for the delayed hippuric acid excretion was considered by Ikeda et al. [159] to be due to a slow step in the conversion of mandelic and phenylglyoxylic acids to hippuric acid. The half-lives of mandelic and phenylglyoxylic acids, and therefore styrene, were estimated to be about 8 hours [159].

In 1981, Pfaffli et al. [160] verified by gas chromatography/mass spectrometry the presence of 4-vinylphenol in the urine of workers in two reinforced plastics factories where average airborne styrene concentrations were about 130 ppm. The correlation between mandelic acid and 4-vinylphenol was good (r=0.93); increasing excretion of mandelic acid was also accompanied by increasing amounts of 4-vinylphenol in the urine. The presence of 4-vinylphenol was not detected in urine of unexposed individuals. The presence of 4-vinylphenol in the urine of styrene workers suggested to the investigators [160] that styrene was also metabolized via arene oxidation, with styrene-3,4-oxide probably functioning as an intermediate. Styrene-3,4-oxide was found in 1982 by Watabe et al. [161] to have potent mutagenicity and cytogenicity toward Salmonella typhimurium strain TA 100. However, other pathways to 4-vinylphenol are possibly present which do not involve arene oxides. The metabolic pathway via the oxidation of the vinyl group is at least quantitatively the more important route as compared to arene oxidation, since the amount of 4-vinylphenol was only about 0.3% of the amount of mandelic acid.

Analytical methods for determining mandelic acid and relationships between urinary mandelic acid concentrations and TWA exposures of workers to styrene are discussed further in Chapter V and in Appendix II.

EFFECTS ON ANIMALS

Toxicity

Effects of styrene vapor exposures at 1,300-10,000 ppm on rats, guinea pigs, rabbits, and monkeys were reported in 1942 by Spencer et al. [53]. The styrene contained 0.01% 4-tert-butylcatechol. Rats (405) and guinea

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pigs (410) were exposed to a series of concentrations during single exposures of various lengths of time. After exposure, the animals were observed for 2-4 weeks, after which some were sacrificed for microscopic study. The responses of animals during exposure to styrene are presented in Table IV-20.

TABLE IV-20

EFFECTS ON RATS AND GUINEA PIGS DURING INHALATION OF STYRENE

Styrene Exposures			Observation During Exposure
ppm	Hours to 100% Mortality		
	Rats	Guinea Pigs	
1,300	>40	40	Rubbing of eyes and nose, violent scratching of face, lacrimation, nasal discharge, salivation, general weakness, unsteadiness after 12-30 hours
2,000	>30	30	As above, but becoming marked after 24-30 hours. Some animals lost consciousness
2,500	21	14	Weakness and stupor followed by incoordination, loss of equilibrium, tremors, unconsciousness after 10-12 hours
5,000	8	8	Weakness, immediate loss of equilibrium, tremors, clonic convulsions, unconsciousness after <1 hour
10,000	3	3	Same as above, with more rapid onset

Taken from Spencer et al. [53]

Local irritation of the eye, nose, and throat and CNS depression manifested by incoordination, loss of equilibrium, tremors, and loss of consciousness were observed during exposure [53]. Findings from examination of the lungs included congestion, frequent hemorrhage, edema, exudation, and varying degrees of leukocytic infiltration. The severity of these effects was greater in guinea pigs than in rats and depended on styrene concentration and duration of exposure. Mild injury to the liver, particularly to the parenchymal cells, and to the kidneys was frequently

observed in rats. Most deaths that occurred during single exposures were attributed to the action of styrene on the central nervous system; delayed deaths were attributed to pneumonia secondary to lung irritation.

The authors [53] concluded that because of the irritating properties of styrene at 1,300 ppm, it was unlikely that humans would tolerate this concentration very long, and that the irritation would serve as an adequate warning of hazardous concentrations.

Guinea pigs, rats, rabbits, and monkeys were exposed to styrene for 7-8 hours a day, 5 days a week for up to 264 exposures by Spencer et al. [53] (see Table IV-21).

TABLE IV-21

EFFECTS OF CHRONIC STYRENE INHALATION ON LABORATORY ANIMALS

Animal		Styrene	No. of	Effects
Species	No.	(ppm)	Exposures	
Rat	28	2,000	105	Marked eye and nose irritation, listlessness, poor weight gain
Guinea pig	12	2,000	98	Marked eye and nose irritation, listlessness, poor weight gain
Rabbit	1	2,000	126	None
Rat	50	1,300	130-139	Eye and nose irritation, increased kidney and liver weight
Guinea pig	94	1,300	130-139	Pronounced lung irritation with congestion, hemorrhage, edema, exudation, and a general acute inflammation; 10% mortality after first few exposures; poor weight gain in survivors
Rabbit	12	1,300	45-264	None
Monkey	4	1,300	262-264	None
Guinea pig	24	650	23-130	None

Taken from Spencer et al. [53]

The authors [53] found no signs of intoxication in rabbits and monkeys after repeated inhalation of styrene at 1,300 ppm. Rats exposed at this concentration for similar periods of time exhibited eye and nose irritation. Guinea pigs exposed at 1,300 ppm exhibited marked lung irritation but were unaffected at 650 ppm.

In a group of 59 rats, Spencer et al. [53] found that those administered styrene orally at 8.0 g/kg all died and those given styrene at 1.6 g/kg all survived. The styrene was emulsified in olive oil with gum arabic. Repeated gastric intubation of styrene at 2.0, 1.0, 0.5, and 0.1 g/kg, given 5 d/wk for 28 days, was also performed. The number of rats given each dose was not given. At 2.0 g/kg, rats died after only a "very few" doses, and pronounced stomach and esophageal irritation was found. Similar irritation and some deaths resulted at 1.0 g/kg. Slight local irritation of the esophagus and stomach and poor weight gains were found in five male rats that survived 20 oral doses of 0.5 g styrene/kg. No differences in unspecified blood components were found between the rats given 0.5 g/kg and the five control rats. Rats that were administered 20 doses of 0.1 g/kg survived and were found to be generally in good health.

After one application of undiluted styrene to the ear of a rabbit, Spencer et al. [53] found "no appreciable reaction." However, after 20 applications over a 4-week period, moderate irritation with blistering and hair loss was observed. Two applications of styrene to the shaved abdomens of rabbits caused marked irritation and some necrosis similar to the effect caused by benzene or toluene [53].

In 1956, Wolf et al. [162] applied undiluted styrene 10-20 times to the ears and shaved abdomens of an unspecified number of rabbits over 2-4 weeks. Skin effects from styrene were characterized by definite erythema of the skin and development of a thin layer of necrotic tissue that resulted in exfoliation. Under the conditions of this experiment, there was no indication that styrene was absorbed through the skin in acutely toxic amounts.

Wolf et al. [162] also placed two drops of liquid styrene on the right eyes of an unspecified number of rabbits. Visual observations of the degree of irritation were made at 3 minutes, 1 hour, 2 days, and 7 days after administration. External corneal injury was visualized with the aid of 5% fluorescein in water. Ocular injury from styrene was manifested by moderate conjunctival irritation, inflammation and slight swelling of the eyelids, and slight transient corneal injury (perceptible superficial necrosis involving less than 50% of the cornea).

Wolf et al. [162] also reported a series of studies on alkylated benzenes, including styrene. After single-dose intubations of 37 rats with 7 ml or less of styrene (undiluted or emulsified in olive oil or corn oil with 5-10% gum arabic), data suggesting an approximate LD50 of 5.0 g/kg were obtained. Upon necropsy, slight liver changes and occasional kidney involvement were observed. Repeated administration of styrene by intubation

(2-3 ml in olive oil, emulsified with gum arabic) to groups of 10 female rats was performed once a day, 5 days per week for 6 months. A group of 20 rats fed only 2.5 ml of olive oil with gum arabic served as controls. One hundred and thirty-two intubations were given at each of the following doses: 66.7, 133, 400, and 667 mg/kg/d. Counts of formed elements of the blood were performed on selected animals from each group after 20, 40, 80, and 130 doses. The examinations included total and differential WBC, total RBC, and hemoglobin content. No effect on rats given styrene was found at 66.7 or 133 mg/kg/d; however, at 400 mg/kg/d, a slight general growth depression and slight liver and kidney weight depressions were reported. These effects were more pronounced when 667 mg/kg/d was administered [162].

In 1968, Gut [163] reported studies of the behavioral effects of styrene on rats. Using spontaneous motor activity as an indicator of behavioral effects, the activity of rats after single exposures to styrene for about 8 hours at 315-1,000 ppm and after repeated exposure concentrations of 228-575 ppm 8 hours per day, 5 days per week for 4-7 weeks was observed. Spontaneous motor activity was measured by the number of movements of the rats in a cage with partitions and doors. All testing was done 8 hours after styrene exposure.

Spontaneous motor activity decreased after a single exposure at 325 ppm. Activity initially decreased after repeated styrene exposures at 345 ppm, but, with further repeated exposures, the effects of styrene weakened and the concentration required to decrease activity rose to more than 985 ppm. Gut [163] stated that the decreased spontaneous motor activity may have been caused by the irritating effects of styrene on the rats, because they often spent time rubbing their eyes and nose rather than moving about in the cage. In 1968, Gut [164] reported further results from this experiment. After 4 weeks, styrene was found to be significantly related ($p<0.001$) to increased relative liver weight in the rats exposed to 325 ppm. However, after 7 weeks of inhalation exposure, no significant change was found in relative liver weight which Gut [164] suggested was due to apparent adaptation by the liver parenchyma.

In 1969, Shugaev [165] reported LC50's of 2,800 ppm for rats exposed to styrene for 4 hours and 4,900 ppm for mice exposed for 2 hours. Styrene content was measured in the tissues of animals that died during exposure at the LC50 to estimate lethal tissue concentrations. Tissue samples (300-500 mg) were extracted with 10 ml of solvent for analysis of styrene by gas chromatography. Concentrations of styrene found in liver, kidney, spleen, perirenal fat, and brain, expressed as milligrams percent of tissue extract, were about 20, 15, 19, 133, and 25 milligrams percent, respectively. The concentration of styrene at the LC50 level in the brains of mice that died during exposure was 18 mg/100 ml.

In 1977, Szulinska et al. [166] exposed 2 groups of 8 male Wistar rats to styrene vapor for 24 hours a day for 172 days. Exposure concentrations were 0.02 and 0.16 ppm as measured using a spectrophotometric method. Blood counts, blood cholinesterase activities, and weights of selected organs

(kidneys, spleen, and liver), expressed as percentages (probably of body weights) were studied, and lungs, liver, spleen, heart, and kidneys were examined microscopically. The investigators [166] described an increased erythrocyte count and a decreased hemoglobin level in the blood (neither significant) in both groups of exposed rats. There were also increases in liver and spleen weight percentages (not significant) for the rats exposed at 0.02 ppm as compared to the controls. The rats exposed at 0.16 ppm had an increased spleen weight percentage and a decreased liver weight percentage (neither significant) as compared to controls. No pathologic changes were found except for an increase in peribronchial tissue in two rats exposed at the higher concentration.

In 1979, Quast et al. [167] administered styrene to Beagle hounds by stomach tube at 200, 400, or 600 mg/kg/day for up to 561 days. Erythrocyte Heinz bodies were found in males dosed with 400 and 600 mg/kg/day, and sporadically in females administered 200 mg/kg/day. Other changes found occasionally were decreased packed cell volume, erythrocyte counts, erythrocyte sedimentation rate, and hemoglobin levels; an increased incidence of anisocytosis and hypochromia of erythrocytes, hemosiderin in reticuloendothelial cells of the liver; and an increased number of hepatocellular intranuclear acidophilic crystalline inclusions. Other blood elements examined were not affected by the administration of styrene at these doses. The blood changes were readily reversed after the administration of styrene was stopped.

Body weight, food consumption, clinical chemistry results, and organ weights (brain, heart, liver, kidneys, and testes) were not affected by the styrene absorption. There were no significant macroscopic or microscopic changes except for the hepatic cells mentioned above, which were attributed to the removal of altered red blood cells. Electron microscopy of peripheral blood and fixed liver tissue confirmed some of the changes detected by light microscopy [167].

In 1978, Seppalainen [168] conducted an experimental study with rats on the peripheral nervous system effects of styrene. Twenty young adult rats were exposed to 300 ppm of styrene, and 15 littermate control rats were sham-exposed in a similar chamber with air circulation. The rats were exposed for 6 hours a day, 5 days per week for up to 11 weeks. A transient increase in the motor conduction velocity of the tail nerve was noted after 6 weeks, but in the comparison to control rats no significant differences were found in measurements taken on rats exposed for 8 and 11 weeks.

In 1979, in another Finnish study, Vainio et al. [169] reported on styrene inhalation in rats. Forty adult male Wistar rats were intermittently exposed for 11 weeks to 300 ppm of styrene 6 hours daily, 5 days per week in a dynamic exposure chamber of 1 cubic meter. The styrene concentration in the chamber air was continuously monitored by infrared analysis. The exposed animals exhibited microscopic liver alterations after 2 weeks, consisting of parenchymal hydropic degeneration, intracellular vacuolization (steatosis), and congestion.

The Chemical Manufacturers Association sponsored a two-year study [170] that was finalized in 1980 on styrene administered in the drinking water of albino rats. Styrene was provided continuously in the drinking water at intended concentrations of 125 and 250 ppm. The approximate daily styrene consumption was estimated to have been, in mg/kg of body weight, 7.7 and 14 for the low- and high-dose males, respectively, and 12 and 21 for the low-and high-dose females, respectively. Initially, there were 50 males and 70 females in each group receiving styrene and 76 males and 106 females as untreated controls. The study [170] concluded that the two-year administration of styrene in the drinking water of rats at these dosage levels resulted in no gross or histological changes. This conclusion was based on evaluation of data on mortality, body weight gain, food and water consumption, hemograms, clinical chemistry, urinalysis, clinical signs (including ophthalmologic observations), gross necropsy findings (including organ weights), and histopathological examination of tissues taken from rats at interim and terminal sacrifice, as well as rats that died on study or were sacrificed in a moribund condition. All tumors encountered among rats dying during the course of the study or at the terminal sacrifice were common spontaneously-occurring tumors of Sprague-Dawley rats, or uncommon tumors that affected only individual rats without regard to treatment group. There were no apparent treatment-related increases in tumor incidence. Also there were no apparent differences between treated and control rats with respect to nontumorous lesions encountered in the study [170].

Mutagenicity

Many studies of the potential mutagenicity of styrene have been performed. Most of these have been tests with microorganisms or mammalian cell cultures *in vitro*, but there have also been some investigations in mammals *in vivo*. Because of the possibility that styrene oxide was an intermediary metabolite of styrene and the likelihood that this epoxide could be mutagenic or carcinogenic, it was also tested for mutagenicity in most of these studies.

In 1976, Vainio et al. [171] studied the mutagenic properties of styrene, styrene oxide, and phenylglycol. These substances were dissolved in absolute ethanol, mixed with agar, and applied to petri dishes. Liver microsomes from rats that had received a polychlorinated biphenyl (PCB) mixture 5 days earlier to stimulate microsomal enzyme activity, and cofactors for generation of reduced nicotinamide adenine dinucleotide phosphate (NADPH), were included in the agar mixture added to some petri dishes to test for indirect mutagenic activity. *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100 were incubated on the petri dishes at 37°C for 2 days, and revertant colonies were counted. Reversion of *S. typhimurium* from histidine auxotrophy to prototrophy was used to indicate mutagenic activity. Phenylglycol was not found to be mutagenic under these conditions. Styrene oxide, however, caused mutations in strains TA 1535 and TA 100, the rate of which was not increased by adding

the microsomal preparation. Therefore, styrene oxide was considered a direct mutagen with the effect due to base substitution. The data on styrene were difficult to interpret because of styrene's toxicity to the organisms, although it seemed to be mutagenic to TA 1535 and TA 100 after metabolic activation [171].

When diethyl maleate (DEM), which depletes cells of cytoplasmic glutathione, or trichloropropane oxide (TCPO), an inhibitor of epoxide hydratase activity, were added to the culture media of TA 1535, only a slight increase in the rate of mutation with styrene in the presence of the enzyme preparation was found. If styrene oxide were the first metabolite of styrene, addition of DEM or TCPO should have resulted in an increase in the concentration of styrene oxide and consequently the rate of mutation, because glutathione depletion or hydratase inhibition should reduce the rate at which the epoxide is inactivated. The authors [171] concluded that a more detailed investigation was warranted. (Epoxide hydratase is often referred to in various reports as epoxide hydrase; this document will uniformly use the former name).

Other investigators [172,173,174,175] have confirmed the mutagenicity of styrene oxide, but have found little evidence that styrene is mutagenic. In 1976, Milvy and Garro [172] tested styrene, styrene oxide, styrene glycol, benzyl alcohol, and mandelic, phenylglyoxylic, benzoic, and hippuric acids by the Ames test using S. typhimurium TA 1535, TA 1537, TA 1538, TA 98, and TA 100. Only styrene oxide was found to be mutagenic under the experimental conditions used [172].

In 1977, Stoltz and Withey [173] also investigated the mutagenicity of styrene and styrene oxide by the Ames test. Using S. typhimurium TA 1535, TA 1537, TA 1538, TA 98, and TA 100 and a liver microsomal preparation from rats or hamsters that had been pretreated with a PCB, styrene was not found to be mutagenic, but there was a dose-dependent increase in the rate of mutations of both TA 1535 and TA 100 due to styrene oxide. The authors [173] concluded that styrene and styrene oxide results differed because of a slow rate of conversion of styrene to styrene oxide and a very rapid rate of removal of styrene oxide due to the action of epoxide hydratase and glutathione-S-transferase.

In 1977, Greim et al. [174] used a modified Ames test using S. typhimurium TA 1535 and TA 1538 and E. coli K12, incubated with and without a liver microsomal preparation that included a NADPH-generating system, to assay the mutagenicity of styrene and styrene oxide. The microsomal fraction was prepared from rat livers that had been pretreated with phenobarbital for 10 days (0.1% in drinking water) or by a single injection (500 mg/kg) of a PCB 4 days before sacrificing. The authors [174] concluded that styrene oxide was mutagenic but styrene was not.

In 1976, Loprieno et al. [175] studied the ability of styrene or styrene oxide to produce forward mutations at 5 loci in the Schizosaccharomyces pombe P1 strain of yeast and in cultured V79 Chinese hamster cells,

and to produce gene conversions at 2 loci in Saccharomyces cerevisiae diploid strain D4 yeast. Host-mediated assays were also performed with the two yeasts. For the in vitro studies, the yeasts were incubated with a purified mouse liver microsome preparation together with NADPH and glucose-6-phosphate dehydrogenase. In the host-mediated assay, male Swiss albino mice were injected intraperitoneally (ip) with yeast cells, and the animals were then treated by gavage with 1 ml of styrene or styrene oxide. Styrene was not active in producing forward mutations in S. pombe or in Chinese hamster V79 cells or in producing gene conversions in S. cerevisiae. In the host-mediated assay, styrene produced gene conversions in S. cerevisiae, but was unable to increase spontaneous forward mutation frequency in S. pombe. As the investigators [175] pointed out, this in vivo mutagenic effect of styrene was produced with a very high dose of styrene, i.e., 1 g/kg. Styrene oxide was active, i.e., mutagenic, in all systems tested except with S. pombe in the host-mediated assay.

Later in 1978, Loprieno et al. [176] investigated the ability of styrene or styrene oxide to induce (1) point mutations in S. typhimurium TA 1535 and in Chinese hamster cells with and without metabolic activation, (2) unscheduled DNA synthesis in heteroploid human cells, and (3) chromosomal changes in mouse bone marrow cells. Styrene was not mutagenic with TA 1535, with or without activation with an S9 mix. Styrene oxide, however, was mutagenic and after activation it was even more so. Styrene was similarly ineffective in the induction of 8-azaguanine resistant mutants in V79 Chinese hamster cells, whether or not activated by an S10 metabolic activation system from mouse liver. Only styrene oxide, and not styrene, each activated by an S10 mix, was able to increase incorporation of tritiated thymidine above background into the DNA of the heteroploid human cells in the presence of an inhibitor of DNA synthesis (hydroxyurea); thus, by this test of unscheduled DNA synthesis, styrene oxide but not styrene was found to be mutagenic. Styrene or styrene oxide was intubated into male and female mice and, after the mice were sacrificed 24 hours later, bone marrow cell preparations were made. Styrene oxide but not styrene caused a statistically significant increase in chromosomal aberrations. Positive controls used in these tests of mutagenicity showed the test systems to be effective. Thus, in this investigation of mutagenicity in several test systems, styrene oxide was consistently found by Loprieno et al. [176] to be mutagenic, while styrene was not.

In 1978, a report by Roberfroid et al. [177] contained data which demonstrated that styrene lowered the Michaelis constant of the enzyme aryl hydrocarbon hydroxylase in Wistar rats in a manner similar to that of benzo(a)pyrene and 3-methylcholanthrene, both of which the investigators considered to be mutagenic and carcinogenic. Styrene caused only about 50 reversions per plate among S. typhimurium TA 1538, while there were about 20 spontaneous reversions. In comparison, benzo(a)pyrene caused about 180 reversions among the same strain, thus suggesting once again that styrene is not more than weakly mutagenic [177]. Earlier, investigators from this laboratory [178] had found styrene not to be mutagenic to S. typhimurium strains TA 98, TA 100, TA 1535, TA 1537, or TA 1538, except that, in the

presence of S9 mix (microsomal enzymes), a reversion to histidine prototrophy was observed with TA 1535 only, suggestive of a base-substitution type of mutation. Styrene oxide caused histidine prototrophy in TA 100 and TA 1535 with or without S9 mix, but did not cause mutations in TA 98, TA 1537, or TA 1538.

In 1978, Linnainmaa et al. [179] studied the effect of styrene and styrene oxide on chromosomes from human lymphocytes. Styrene was incubated with a lymphocyte preparation for 72 hours, and styrene oxide for a shorter time. A total of 100 metaphases or 100 anaphases were examined at each concentration of styrene or styrene oxide for cytogenetic aberrations, and 1,000 interphase nuclei were examined for the presence of micronuclei and nuclear bridges.

Styrene mainly caused chromosome breaks (19 breaks/100 metaphases, $p<0.001$); styrene oxide was primarily responsible for the formation of micronuclei and nuclear bridges (38 micronuclei/1,000 interphase cells, $p<0.001$). Linnainmaa et al. [179] suggested that impurities in the styrene preparation might have been responsible for the results that differed from those of styrene oxide. They reported that the styrene contained 0.60 ppm ethylbenzene, 0.75 ppm alpha-methyl styrene, and 0.50 ppm styrene oxide, but did not test all of these contaminants for mutagenicity. The investigators [179] speculated that the chromosome breaks they observed were due to formation of styrene oxide or possibly to the presence of the alleged metabolite [160,180] styrene-3,4-oxide.

In a later study by this same group in 1980, Norppa et al. [181] found that styrene and styrene oxide showed a clear dose-response relationship in the induction of sister chromatid exchanges (SCE) in human whole blood lymphocyte cultures. To find out whether the potential of styrene to induce SCE was accompanied by metabolic conversion to styrene oxide, gas chromatographic analyses were carried out in human lymphocyte cultures after 0.5, 2, 6, and 24 hours after treatment with styrene and styrene oxide. In the styrene-treated cultures, the ratio of styrene oxide to styrene was progressively increased with incubation time. In styrene-treated control cultures without blood, there was no increase of styrene oxide. In the styrene oxide-treated cultures, the amount of styrene oxide gradually decreased with incubation time. The investigators [181] concluded that styrene oxide could be formed from styrene in human cells but that it was not clear which cells in human blood were responsible for the metabolic activation of styrene.

In 1978, De Raat [182] tested the ability of styrene and its presumed metabolite styrene oxide to induce SCE in Chinese hamster ovarian cells with and without metabolic activation. Styrene oxide appeared to be a potent inducer of SCE. Styrene in doses up to 1.0 ml/l did not increase the number of SCE per metaphase, even with metabolic activation. Induction of SCE by styrene in the presence of metabolic activation only occurred when cyclohexene oxide was used as an inhibitor of the enzyme epoxide hydratase. De Raat [182] interpreted the lack of induction of SCE by styrene in the

presence of metabolic activation as being caused by a very rapid biotransformation of styrene oxide, clearly a compound that induces SCE, rather than styrene not being converted to its oxide.

There is some in vivo experimental evidence in rodents and flies that styrene itself can cause mutations. In 1980, Conner et al. [183] exposed 3-4 mice for 6 hours per day to styrene vapor concentrations ranging from 104-922 ppm for 4 days and at 920 ppm for 1 and 2 days. An increased SCE frequency was found in regenerating liver cells, in bone marrow cells, and in alveolar macrophages. Some of the mice had two-thirds of their liver removed surgically a day prior to the first exposure. On the last day of styrene exposure, the mice were injected with 5-bromodeoxyuridine; on the following morning, they were injected with colchicine and sacrificed several hours later. The SCE frequencies in regenerating liver cells, bone marrow cells, and alveolar macrophages of hepatectomized mice exposed to styrene at 387, 591, and 922 ppm for 4 days and in bone marrow cells and alveolar macrophages from nonhepatectomized mice exposed to styrene at 591 and 922 ppm for 4 days were statistically greater ($p<0.05$) than those in the controls. There was also a significant increase ($p<0.001$) in cell frequency in regenerating liver, bone marrow, and alveolar macrophage cells from both hepatectomized and nonhepatectomized mice exposed for 2 days at 922 ppm but not in those exposed for 1 day at that concentration.

In 1980, Meretoja et al. [184] found clastogenic effects in bone marrow cells of rats. Male rats were exposed to styrene vapor at 300 ppm for 6 hours per day, 5 days per week, for 2-11 weeks. Animals were sacrificed weekly, and bone marrow tissue was taken from the femur. A total of 100 metaphases per animal were examined for aneuploidy and chromosomal aberrations. A significant increase in chromosomal aberrations appeared after 9 weeks of exposure. Most of the aberrations were chromosomal breaks, but there were also a few chromatid breaks. The incidence of aberrant cells was 8-12% in exposed animals and 1-6% in controls. Polyploid cells were found in every sample preparation from the rats exposed to styrene for 11 weeks.

However, in another investigation by these researchers, published in 1980 by Norppa et al. [185], styrene was not found to cause clastogenic effects in bone marrow cells of hamsters. Male Chinese hamsters, 3-4 months old, were exposed to styrene vapor at 300 ppm for 6 hours per day. One group of 4 hamsters was exposed for 4 days, the other group of 4 was exposed 5 days per week for 3 weeks. The investigators [185] analyzed 100 bone marrow metaphases from each animal for chromosome or chromatid aberrations and gaps. No significant difference from controls was found in either styrene-exposed group. The effect of ethanol, alone and with styrene, was also studied. Animals receiving both 300 ppm of styrene and ethanol (15% v/v in drinking water, ad libitum) for 4 days had significantly more chromosomal aberrations, not including gaps, than did controls or hamsters administered only styrene, but not more than hamsters given only ethanol. The incidence of gaps was not significantly different among the groups. No significant differences among the several groups treated for 3 weeks were found, either in aberrations or in gaps [185].

In vivo inhalation exposure of male Chinese hamsters to styrene oxide (25, 50, 75, and 100 ppm) was reported in 1979 by these same investigators (Norppa et al. [186]) to have no effects on chromosomal aberration rates or frequencies of SCE in bone marrow cells. The only positive response in chromosome aberration frequency was obtained when styrene was injected ip in a lethal concentration (500 mg/kg body weight); 1 of 6 hamsters showed slightly elevated values of SCE after this high dose.

In 1979, Donner et al. [187] reported that styrene and styrene oxide caused recessive lethal mutations in fruit flies. Drosophila melanogaster were exposed to styrene oxide vapor at 200 ppm for 6 hours per day for 4 days, or to styrene by being fed for 24 hours on tissue paper moistened with 10 ml of a solution containing styrene at 200 ppm in 1% aqueous sucrose. The fruit flies were pretreated either with phenobarbital, to induce metabolizing enzymes, or, in the case of flies exposed to styrene oxide, with trichloropropane oxide (TCPO), to inhibit epoxide hydratase. Both styrene and styrene oxide produced a significant increase in recessive lethal mutations. Neither pretreatment showed mutagenic potency, but the frequency of recessive lethal mutations from styrene or styrene oxide was doubled by phenobarbital pretreatment; also, in fruit flies exposed to styrene oxide, pretreatment by an epoxide hydratase inhibitor (TCPO) increased the mutation rate about two-fold over that caused by styrene oxide alone [187].

Reproductive Effects

There have been a number of experimental animal studies investigating possible reproductive effects of exposure to styrene. In 1977, Vainio et al. [188] investigated the toxicity of styrene and styrene oxide toward chicken embryos from White-Leghorn SK12 chickens. Various amounts of the compounds in 50 µl of an olive oil-ethanol mixture were injected into the air sacs of the eggs. For control purposes, 50 µl of the olive oil-ethanol vehicle were injected into other eggs.

After incubation for 14 days at 37°C, 80-90% of the control embryos were alive, but no embryos survived that had received 100 µmol of styrene. Of those embryos that received 50 µmol of styrene, only 30% survived; with 2 µmol, 90% survived. Malformations were found in about 15% of the embryos that had received styrene and in about 7% of those that had received styrene oxide. Vainio et al. [188] determined that the embryos were most susceptible to the toxic effects of styrene and styrene oxide on the day of, and the day after, the beginning of incubation.

In 1974, Zlobina et al. [189] reported studies of styrene concentrations in rat maternal and fetal blood and in amniotic fluid after a 2-hour exposure to styrene vapor (3.6 or 10 ppm). Placental styrene concentrations were not determined. The results presented in Table Iv-22 demonstrate that styrene can cross the placenta.

TABLE IV-22

CONCENTRATION OF STYRENE IN MATERNAL BLOOD, FETAL BLOOD, AND AMNIOTIC FLUID IN 18- TO 21-DAY RAT FETUSES

Styrene Exposure	Styrene Concentration, µg/ml		
	Maternal Blood	Fetal Blood	Amniotic Fluid
10 ppm	10.95-12.25	8-8.8	2.35-2.8
3.6 ppm	1.07-2.62	0.9-1.65	1.25-1.8

Adapted from Zlobina et al. [189]

In 1974, Ragul'ye [190] reported the effects of maternal styrene inhalation exposures on the development of the embryo. In one study, 23 pregnant albino rats were exposed at 1.2 or 12 ppm of styrene for 4 hours per day throughout gestation (21 days); there was a control group of 15 rats. Numbers of live embryos, stillbirths, resorptions, and implantation sites, together with embryo mortality, pre- and post-implantation deaths, and embryo weight and size were studied. In addition, RBC, WBC, hemoglobin, oxygen consumption, and respiratory rate of the dams were measured on the 15th to 17th day of gestation and compared to pre-exposure findings.

Maternal exposure to styrene at 12 ppm significantly increased pre-implantation loss (20.7 vs. 3.6 in controls) as well as total embryo mortality (25.2 vs. 15.5 in controls); no significant changes were found in the other indices. No significant changes in any indices studied were found in the rats exposed at 1.2 ppm. There was no pathological embryo development observed in either experimental group. Ragul'ye [190] also reported a significant increase in deaths/litter during the first 2 weeks of life (1.66 and 0.6 in the rats exposed at 12 and 1.2 ppm, respectively, vs. 0 in the controls).

Ragul'ye [190] also exposed 10 pregnant rats to styrene at 1.2 ppm and 10 other pregnant rats at 0.4 ppm for 4 hours per day for 21 days (the entire gestation period). At the same concentrations, two other groups of 10 pregnant rats each were exposed, but only during the first 7 days of gestation. Twenty pregnant rats served as controls. All rats were sacrificed on the 21st day of gestation.

In the rats exposed for the entire gestation period, the rate of resorptions/dam was 0.2 for those exposed at 0.4 ppm, 1.3 for those exposed at 1.2 ppm, and 0 for the control group. There was also a higher rate of resorptions/dam (0.66) found in rats exposed at 1.2 ppm for the first 7 days of gestation, with none in the control group. Other significant results included an increased embryonic mortality in litters of dams exposed at 1.2 ppm for the entire gestation period (12.8% vs. 2.5%), an increased number of pre-implantation deaths at exposures to 1.2 and 0.4 ppm for the entire gestation period and during the first 7 days, an increased number of post-implantation deaths in both groups exposed for the entire gestation period, and a decreased embryo size and weight among rats exposed at 1.2 ppm for the entire gestation period [190]. All litters examined appeared to have been first litters.

Ragul'ye [190], who did not state the levels of statistical significance, gave no data other than means and an undescribed index of variation. The description of how pre-implantation and total embryo losses were measured was not given; however, observation of corpora lutea, resorption sites, and total births seems the obvious method. Had the data or a description of methods been given, it would be possible to be more certain of the meaning of total embryo mortality; most likely, this term was used to mean a total of pre- and post-implantation losses. (The word translated as embryo is interpreted to have been applied to all stages of prenatal development, from blastocyst through fetus.)

In 1979, Vergiyeva et al. [191] studied embryotoxicity in rats in an investigation designed at least in part to check on the results of Ragul'ye [190]. Three groups of pregnant rats were exposed to styrene vapor 4 hours per day, 5 days per week. Groups I and II were exposed at 47 ppm on days 2-21 of gestation; group III was exposed at 165 ppm on days 2-16 of gestation. Progeny from dams of groups I and III were observed for 90 days after birth. Dams from group II were sacrificed on the 21st day; maternal weights, numbers of corpora lutea, resorptions and autolysis, the number and weights of live pups, and structural anomalies were recorded.

There were no changes from controls in the experimental animals as to the course, duration, and outcome of pregnancies or in indices such as implantations, resorptions, and live and still births. Dams and progenies kept for 90 days after birth did not differ significantly from controls in hemoglobin and RBC, in hexobarbital sleeping time one month after birth, or in behavioral tests consisting of an open field test and a measured reaction to loud noise. Methods of studying structural anomalies were not described, but the investigators [191] stated none were found in either controls or Group II progeny.

Vergiyeva et al. [191] gave a few more details of methods and results than did Ragul'ye [190] and, especially because it described exposures of rats at higher concentrations without evidence of embryotoxicity, this study is taken as refuting the implications of embryotoxicity found at low concentrations of styrene in the earlier report [190].

In 1978, Murray et al. [192] investigated possible styrene teratogenicity in rats and rabbits. Groups of 29 or 30 Sprague-Dawley rats and 20 New Zealand white rabbits were exposed to styrene vapor for 7 hours per day from day 6 of pregnancy through day 15 (rats) or day 18 (rabbits). Exposure levels were 0, 300, or 600 ppm styrene. In addition, other rats were intubated with styrene in peanut oil at 0, 90, or 150 mg/kg twice daily on days 6 through 15 of gestation. There were no significant changes ($p<0.05$) in the exposed animals as compared with controls during gestation except for a reduced weight gain on days 6 through 9 of gestation in rats (inhalation and gavage treatments) associated with a decreased food consumption, and increased water consumption on days 9 through 20 of gestation by rats (inhalation treatment). Dams were sacrificed just prior to expected delivery, and fetuses were examined. There was a statistically significant increase ($p<0.05$) in fetal crown-rump length in litters from rats exposed at 300 ppm but not at 600 ppm. Mean crown-rump length of intubated rats was similar to that of controls. External, visceral, and skeletal malformations did not significantly differ in incidence from matched or historical controls. There were no significant changes ($p<0.05$) seen in rabbits except for the incidence of unossified fifth sternebrae among litters from rabbits exposed at 600 ppm; however, this incidence was similar to that seen in control groups from other recent studies. Because of this and because the change in rat fetal size at 300 ppm was not dose-related and the incidence of skeletal changes in rats were not different from controls, it seems inappropriate, from the evidence in this study, to draw conclusions that styrene is teratogenic or otherwise embryotoxic at these levels.

In 1980, Kankaanpaa et al. [193] exposed pregnant BMR/T6T6 mice and Chinese hamsters to styrene vapor and examined possible changes in fetal development. Pregnant mice were exposed at 250 ppm for 6 hours per day on days 6 through 16 of gestation, and were sacrificed for examination of fetuses after the day 16 exposure. Chinese hamsters were exposed 6 hours per day on days 6 through 18 of gestation, but the exposure concentrations were 300, 500, 750, or 1,000 ppm. There were no significant differences in ratios of live fetuses to total litter size, in numbers of dead or resorbed fetuses, or in numbers of malformed fetuses in either species, except that there was a significant excess ($p<0.001$) of dead or resorbed fetuses from hamsters exposed at 1,000 ppm and there was a nonsignificant excess of dead or resorbed fetuses from mice. There were also more malformations (rib fusion and extra ribs) in exposed mice, but the statistical significance was not described. This study [193] suggests embryotoxicity at high exposure levels, but is consistent with results of other studies [190,191,192] in failing to find a significant excess of terata from styrene exposure.

A report [170] of a three-generation reproductive study on styrene administered in the drinking water of rats was finalized in 1980. It was part of the study sponsored by the Chemical Manufacturers Association that was discussed earlier in the Toxicity Section. At least 10 males and 20 females (F0 generation) from each group of the chronic study (those dosed at 125 or 250 ppm, and controls) were mated to produce F1 pups. At breeding

age, the F1 rats were mated within their respective dose groups to produce F2 litters, and these rats in turn produced F3 pups. Styrene treatment in drinking water was maintained throughout.

The report of the study [170] concluded that styrene administered in the drinking water had no deleterious effects on the reproductive capacity of rats through three generations. The conclusion was based on evaluation (for each generation of each dose group) of fertility indices, mean litter size, live-to-total pup ratios, pup survival indices at intervals from birth to weaning, liver and kidney weights of representative pups necropsied at weaning, cytogenetic evaluation of bone marrow samples of other weanlings, and gross necropsy of F1 and F2 parents, including organ weights. In addition, histopathologic examinations were made of liver and kidneys of weanlings and of tissues of representative F1 and F2 parents.

In 1981, Sikov et al. [194] assessed the teratogenic effects of styrene oxide inhalation on rats and rabbits. Rats were exposed to 100 or 300 ppm for 7 hours per day, 5 days per week for 3 weeks before being mated and exposed daily through 19 days of gestation. Rabbits were artificially inseminated and exposed for 7 hours daily through the 24th day of gestation. The rats were sacrificed at the 21st day of gestation and the rabbits at the 30th day of gestation. Pregnant animals were examined for toxic changes including altered tissue weights and histopathological effects. Litters were examined for embryotoxicity and live fetuses were examined for external, visceral, and skeletal malformations. There was extensive mortality in rats that received prolonged exposure to 100 ppm styrene oxide, and 300 ppm was so rapidly lethal that exposures were terminated. Lower concentrations (15 and 50 ppm) were used for exposure of the rabbits; 50 ppm styrene oxide produced 79% mortality. Gestational exposure appeared to decrease fecundity by increasing loss of embryos before implantation in rats, and tended to increase the incidence of resorptions in rabbits. In both species, fetal weights and lengths were reduced by gestational exposure. The incidence of ossification defects of the sternebrae and occipital bones was increased by gestational exposure of rats to styrene oxide [194].

Carcinogenicity

There have a been a number of experimental animal studies investigating the long-term effects of styrene. In 1978, Jersey et al. [195] conducted an inhalation study of male and female Sprague-Dawley rats exposed at 600 or 1,200 ppm, the higher concentration being reduced to 1,000 ppm after 2 months because of excessive toxicity in the male rats. Male rats were exposed for more than 18 months and female rats for almost 21 months. Exposure periods were 6 hours per day, 5 days per week. All survivors were sacrificed for necropsy at 24 months. There were reduced weight gains in all exposed groups of rats except in females exposed at 600 ppm. Female rats at the higher concentration had increased liver weights and a higher incidence of alveolar histiocytosis in their lungs. Male rats in the control group and those exposed to styrene at the higher concentration had excessive mortality from an intercurrent disease, chronic murine pneumonia. There was no evidence of tumors in the male rats attributable to the exposure regimen. The female rats in both exposure groups had an increase (though not significant) in the combined frequency rate of tumors in the leukemia and lymphosarcoma classifications. The investigators [195] believed that the exposure concentrations used overwhelmed the ability of the rats to detoxify styrene; because of this, the high incidence of spontaneous disease, and the equivocal results, they recommended that a new study be initiated.

In 1978, Ponomarkov and Tomatis [196] investigated the long-term effects of styrene in 020 and C57 B1 mice and BD IV rats. Styrene dissolved in olive oil was administered by stomach tube; other groups of mice and rats were given only olive oil, and others were not treated. All animals were fed a commercial food preparation that had been analyzed for aflatoxins, which were absent, and nitrosamines, which were present at 0.2-0.6 ppb.

Each of 29 pregnant 020 mice was administered 1,350 mg styrene/kg on the 17th day of gestation. Nine other pregnant females were given 0.1 ml of olive oil only on the same day. After weaning, their progeny received the same dose once a week; treatment with styrene was stopped after 16 weeks because of the toxicity of styrene. Offspring (54 male and 47 female mice) of untreated dams received no treatment [196].

For 020 mice, pre-weaning mortality was significantly greater among the styrene-treated animals than among olive oil-treated animals (43% vs. 22%). Higher mortality continued even after treatment with styrene had ended. The average age of styrene-treated mice at death was 32 weeks for males and 49 weeks for females, compared with 88 and 85 weeks for olive oil-treated male and female mice and 94 and 99 weeks for untreated male and female mice, respectively [196].

Multiple centrilobular necrosis of the liver, hypoplasia of the spleen, and severe congestion of the lungs were the most frequently observed lesions

in styrene-treated O20 mice which died within the first 20 weeks [196]. Extensive inflammation around necrotic foci was often observed in the livers of styrene-treated mice that died up to the 45th week of treatment; bronchitis and peribronchitis were also frequently observed. Animals that died after 45 weeks had what the authors [196] described as multiple abscess-like round cavities in the liver that were filled with polymorphonuclear leukocytes and were surrounded by connective tissue capsules. Calcium deposits were also observed.

The percentage of tumor-bearing, singly-dosed, styrene-treated dams did not differ from the group treated only with olive oil. Among their offspring, however, 89% of the males and 100% of the females treated with styrene had lung tumors compared with 42% of the males and 67% of the females of the olive oil-treated controls, both statistically significant differences ($p<0.01$). When styrene-treated O20 mice were compared with untreated animals, the incidence of lung tumors was significantly greater ($p<0.001$) only in styrene-treated females.

Average age at death of the lung tumor-bearing O20 mice was 49 weeks for male and 58 weeks for female styrene-treated mice, 84 and 85 weeks for olive oil-treated males and females, and 87 and 91 weeks for untreated male and females, respectively. The lung tumors were histologically identified as either adenomas or adenocarcinomas. The incidences of lung tumors in olive oil-treated and untreated animals at sites other than the lungs were greater than the incidences in styrene-treated mice, perhaps, as the authors [196] commented, because of the longer survival of the controls.

Styrene (300 mg/kg in 0.1 ml olive oil) was also given to each of 15 pregnant C57 Bl mice on the 17th day of gestation; their progeny received the same dose after weaning weekly for life, up to 120 weeks. For controls, 0.1 ml olive oil was administered after weaning weekly to the offspring (12 males and 13 females) of five pregnant mice given 0.1 ml olive oil on the 17th day of pregnancy; 51 males and 49 females served as untreated controls [196].

For C57 Bl mice there was an increase, though not statistically significant, in the incidence of tumors, mainly lymphomas, in dams singly dosed with styrene. There were three hepatocellular carcinomas in the styrene-treated mice and one hepatocellular adenoma each in an olive oil-treated mouse and in an untreated mouse. Unlike the O20 mice, there were no significant differences in mortality, life-span, or body weights between the C57 Bl mice treated with styrene and those treated with olive oil.

On the 17th day of gestation, each of 21 pregnant BD IV rats were administered 1,350 mg styrene/kg in olive oil. Their progeny, 73 males and 71 females, each received 500 mg styrene/kg weekly for 120 weeks after weaning. Ten pregnant BD IV rats received only olive oil (0.3 ml) and their progeny (36 males and 39 females) were given 0.3 ml olive oil weekly after weaning. Untreated controls were not used [196].

Average litter sizes of the BD IV rats were similar, but offspring of styrene-treated dams had a greater pre-weaning mortality than did the olive oil-treated dams (10% vs. 2.5%); the difference was not significant. In some styrene-treated animals that died between weeks 50 and 60, the investigators [196] found moderate congestion of the lungs and kidneys and small necrotic foci in liver parenchyma. Although liver damage was not observed in animals that died between weeks 80 and 90, lesions of the forestomach (atrophy or desquamation of epithelium, and necrotic areas with inflammation) and of the kidney (hyperplasia of the pelvis epithelium) were frequently noted.

The percentage of tumor-bearing BD IV dams given a single dose of styrene during pregnancy was greater than that in the olive oil-treated group (65% vs. 50%); this difference was not statistically significant. The percentage of tumor-bearing, styrene-treated progeny was not significantly different from that of the olive oil-treated controls (24% vs. 39%). There were, however, a few tumors in styrene-treated rats which were not observed in the control animals, namely three neurogenic and three stomach tumors. Ponomarkov and Tomatis [196] concluded that their results provided weak evidence of the carcinogenicity of styrene in one of the two strains of mice tested, when it was given at a high dose level.

In 1979, under the program of the National Cancer Institute (NCI) for testing possible carcinogenicity, Fischer 344 rats and B6C3F1 mice were given styrene in corn oil by stomach tube [197]. The animals were intubated 5 days a week for up to 103 weeks in the case of rats administered the lowest dose and up to 78 weeks in all other groups. Surviving rats were sacrificed for necropsy at 104-105 weeks, and mice at 91 weeks. There were 50 rats of each sex at each of 3 doses (500, 1,000, and 2,000 mg/kg) and 40 of each sex given only the corn oil vehicle. There were 50 mice of each sex at each of two doses (150 and 300 mg/kg) and 20 of each sex given only the corn oil vehicle.

In male mice, there was an excess incidence of lung adenomas and carcinomas compared with vehicle controls but not compared with historical controls at NCI. There was no significant excess of tumors in rats, but so few male and female rats survived on the highest dose that there were limited numbers of these animals at risk of developing neoplasms. NCI [197] concluded that under the conditions of the bioassay the data (i.e., excesses of lung adenomas and carcinomas) provided "suggestive" evidence for the carcinogenicity of styrene in male B6C3F1 mice, but did not provide "convincing" evidence for the carcinogenicity of styrene in Fischer 344 rats or B6C3F1 mice of either sex.

In 1979, in a companion experiment by NCI [198], a solution of beta-nitrostyrene, consisting of 30% nitrostyrene and 70% styrene, was dissolved in corn oil and intubated into Fischer 344 rats and B6C3F1 mice. The beta-nitrostyrene doses were 150 and 300 mg/kg for male rats; 75 and 150 mg/kg for female rats; and 87.5 and 175 mg/kg for mice of both sexes. Doses of styrene, then, in addition, were 350 and 700 mg/kg for the male rats; 175

and 350 mg/kg for the female rats; and 204 and 408 mg/kg for the mice. The doses were administered 3 days a week for 78-79 weeks, after which mice were held an additional 14 weeks and the rats an additional 29 weeks before survivors were sacrificed for necropsy.

When the incidences of alveolar and bronchiolar adenomas and carcinomas were combined, there was a significant excess in low-dose male mice compared to the corn oil vehicle controls by the Fisher exact comparison ($p=0.016$), but not by the Cochran-Armitage test. There was no significant excess in high-dose male mice found by either test. No other significant excess in tumors was found. NCI [198] concluded that under the conditions of the bioassay, there was no "convincing" evidence for the carcinogenicity of a solution of beta-nitrostyrene and styrene in Fischer 344 rats or B6C3F1 mice.

Studies of the potential carcinogenicity of styrene oxide were reported by Kotin and Falk [199], Van Duuren et al. [200], Weil et al. [201], and by Maltoni et al. [202]. In 1963, Kotin and Falk [199] reported that, 11 months after administering 20 μmoles of styrene oxide by an unspecified route to 30 C3H mice, there were 3 malignant lymphomas (16%) among the 19 survivors. The cause of death in these mice was not stated, nor was the time when they died. The use of controls was also not reported.

In 1963, Van Duuren et al. [200] studied possible tumor formation from styrene oxide in male Swiss-Millerton mice. Thirty animals were tested with 10% styrene oxide in benzene that was topically applied. The mice, 8 weeks old at the onset of the experiment, had their backs painted three times a week with approximately 100 mg of solution/application. After a median survival time of 431 days, three styrene oxide treated mice (10%) were found to have tumors (type not specified), one of which was considered cancerous. Control groups were painted with either benzene or acetone. Positive controls received 100 mg of benzo(a)pyrene in benzene or acetone; negative controls received no treatment. Incidence of tumors in the controls was: (a) benzene group, 11/150 mice (7%), 10 had papillomas, and 1 developed cancer; (b) acetone group, 7/120 mice (6%) had papillomas; (c) benzo(a)pyrene in benzene (positive control), 49/90 mice (54%) developed tumors, 26 of which were cancerous; and (d) benzo(a)pyrene in acetone (positive control), 83/120 mice (69%) developed tumors, 49 of which were cancerous. Of the 267 untreated controls, 5% developed tumors, 1 of which was a squamous cell cancer, as compared with the long-term incidence of tumors in untreated Swiss-Millerton mice in the laboratory of 1.4%, (all squamous papillomas). Because the incidence of tumors in mice administered styrene oxide in benzene was not significantly greater than the incidence due to benzene application alone, this experiment does not give evidence that styrene oxide is tumorigenic.

In 1963, Weil et al. [201] studied the possible carcinogenicity of various epoxides in mice. Styrene oxide dissolved in acetone was applied by brush three times a week to the shaved backs of two groups of C3H mice that were 90 days old when the experiment began. One group was treated with a solution containing 10% styrene oxide and the other with a solution

containing 5%. The number of mice initially in the group that received 10% styrene oxide was not reported, but 18 were in the group at 12 months and 2 were still alive at 24 months. The maximum number of months the mice in the 10% group were painted was 18. No tumors were found in the group treated with 10% styrene oxide. Forty mice were initially present in the group treated with 5% styrene oxide; 35 were alive at 17 months and 17 were still alive at 24 months. Administration of styrene oxide continued through this period, and no tumors were found [201]. This experiment provides some evidence, albeit in small groups of mice, that styrene oxide is not tumorigenic by topical application.

In 1979, Maltoni et al. [202] reported that styrene oxide caused stomach epithelial tumors in rats. Styrene oxide was administered in olive oil by stomach tube at two dose levels, 50 and 250 mg/kg, to Sprague-Dawley rats once per day, 4-5 days per week, for 52 weeks, after which the animals were allowed to live until their natural deaths. Controls were intubated with olive oil alone. Papillomas and carcinomas, both in situ and invasive, were observed in the forestomachs of the rats at both dose levels at an incidence significantly greater than controls and with an evident dose-response relationship. Many of the carcinomas had metastasized to the liver. Rats with or without tumors of the forestomach often had precursor lesions. Maltoni et al. [202] commented that epithelial tumors of the forestomach were rare in this strain of rat, and concluded that styrene oxide was carcinogenic, affecting the organ "most directly exposed."

Uptake, Metabolism, and Elimination

In 1954, Danishefsky and Willhite [203] reported a study of the metabolism of styrene in Wistar rats. Styrene labeled with carbon-14 at the 8 position (8-14C styrene) was dissolved in peanut oil to make a 20% solution. Each rat was injected subcutaneously with 0.1 ml of the radioactive solution. Distribution of the isotope in tissues was determined 1, 6, and 24 hours after injection. Exhaled carbon dioxide, urine, feces, and expired styrene were collected and analyzed for carbon-14. After 1 hour, the liver, kidneys, blood, and urine had the highest radioactivity. Styrene was rapidly metabolized and excreted primarily in the urine. Six hours after administration, 37% of the initial radioactivity was found in the urine and 6% in expired carbon dioxide. After 24 hours, 71.0% of the radioactivity had been excreted in the urine, 11.8% in expired carbon dioxide, 2.6% in the feces, and 2.9% as unchanged expired styrene. Although the finding of labeled carbon dioxide indicates cleavage of the vinyl moiety of styrene, it does not distinguish initial cleavage of the terminal carbon from that of the entire vinyl group.

In 1969, Shugaev [165] exposed rats to styrene for 1 hour at 2,800 ppm (the LC50 for 4 hours). The animals were sacrificed at various times after exposure and brains and livers were removed and extracted for determination of styrene levels. Data are presented in Table IV-23.

TABLE IV-23

AVERAGE CONCENTRATION OF STYRENE IN THE BRAIN AND LIVER OF RATS AFTER EXPOSURE TO STYRENE AT 2,800 PPM FOR ONE HOUR

Time After Removal From Exposure (min)	AVERAGE STYRENE CONCENTRATION Brain mg/100 ml Extract	Liver mg/100 ml Extract
0.1	21.8	20.2
15	22.2	23.5
30	17.7	19.1
60	8.6	12.8
90	Trace-4.4	6.8

Taken from Shugaev [165]

Shugaev [165] found that styrene was more slowly removed from the organs than butadiene or hexene and that the anesthetic effects of styrene lasted longer than similar effects from the other compounds. Shugaev [165] also found that near-lethal concentrations of styrene were absorbed when tails of rats were immersed in liquid styrene for 1 hour (precautions had been taken to avoid styrene inhalation). Styrene concentrations of 11.1-17.3 mg/100 ml extract in the brain were found in rats sacrificed immediately after the exposure ended.

In 1977, Savolainen and Vainio [204] conducted an investigation of 14C-styrene and tritiated(3H)-styrene oxide injected ip into adult male Sprague-Dawley rats. Ten rats each received 460 µmol of styrene oxide and 15 each received 577 µmol of styrene. Each compound was dissolved in 1 ml of olive oil for administration. Three and six hours after injection of styrene oxide, 5 rats each were sacrificed. The same procedure was followed after injection of styrene, and in addition, five rats were sacrificed 24 hours after injection. The blood, brain, spinal cord, liver, duodenum, lungs, and kidneys were removed for analysis of radioactivity and separation into protein, water-soluble, and lipid (brain only) fractions. Radioactivity (14C) in blood after styrene injection increased from 3 to 6 hours, but remained approximately constant in the liver, lungs, kidneys, duodenum, brain, and spinal cord. Radioactivity (3H) from styrene oxide decreased in the liver and kidneys from 3 to 6 hours after injection, but remained constant in all other organs. After styrene injection, about 91% of the radioactivity in the brain was found in the water-soluble and chloroform-methanol-soluble fractions. After styrene oxide injection, about

83% of the radioactivity was found in the water-soluble fraction. The investigators [204] did not consider that the observed differences might have been due to the different isotopes used. Because tritium readily exchanges with hydrogen of other molecules, particularly proteins, nucleic acids, and water, it would be necessary to isolate and identify suspected metabolites of styrene and styrene oxide.

In 1978, Plotnick and Weigel [205] studied the tissue distribution and excretion of uniformly ring-labeled-14C-styrene in male and female Sprague-Dawley rats at various time intervals following a single oral dose of 20 mg/kg. Peak tissue levels of radioactivity were achieved at or before 4 hours after administration. The organ with the highest concentration of radioactivity at all time intervals studied (2, 4, 8, 12, and 24 hours), and in both sexes, was the kidney, followed in order of decreasing concentration by the liver and pancreas. Approximately 90% of the radioactivity administered was excreted in the urine within 24 hours of administration. Less than 2% of the dose was found in the feces. The investigators [205] speculated that the high levels found in the pancreas might be related to increased glucose tolerance, which has been reported in some styrene workers [115,116,120].

In 1976, Sauerhoff et al. investigated the metabolism and distribution of styrene in adult Sprague-Dawley rats after oral administration of a single dose of 50 or 500 mg styrene/kg [206] and after exposure to styrene vapor at 60 or 600 ppm for 6 hours [207]. For both investigations, 14C-styrene (uniformly ring-labeled) was used and the animals were sacrificed 72 hours after exposure. Radioactivity recovered in the urine, feces, expired air, and carcass was about 95, 4, 1.5, and 0%, respectively, after the oral dose of 50 mg/kg and about 90, 1.5, 9, and 0%, respectively, after the 500 mg/kg dose. In both cases, the percentage of radioactivity in expired air was lower in female than in male rats (0.9 vs. 1.8% and 5.3 vs. 12% at 50 and 500 mg/kg, respectively), indicating that female rats retained styrene longer than male rats [206].

After a dose of 50 mg/kg, six 14C-labeled metabolites were found in the urine. After a dose of 500 mg/kg or exposure at 60 or 600 ppm, seven radioactive metabolites were found. After all doses and exposures, four of these metabolites were identified as phenylglyoxylic, mandelic, benzoic, and hippuric acids. The recovered radioactivity associated with phenylglyoxylic, mandelic, benzoic, and hippuric acids was about 33, 30, 1.5, and 18%, respectively, in male rats; in females, it was about 25, 41, 2, and 20%, respectively [206,207].

In 1978, in a later investigation by Ramsey and Young [208] at the same laboratory as Sauerhoff et al. [206,207], adult rats were exposed to styrene vapor at 80, 200, 600, or 1,200 ppm for up to 24 hours. Styrene concentrations in the blood of rats were measured during and after a 6-hour exposure. The investigators [208] concluded that styrene at exposures up to 200 ppm did not accumulate in the body. Styrene was highly concentrated in fat relative to blood; the ratio of the concentration of styrene in fat to that in blood was approximately 40:1 at 80 ppm and 80:1 at 1,200 ppm.

In 1978, Savolainen and Pfaffli [209] exposed male rats to styrene vapor at 300 ppm for 6 hours per day, 5 days per week, for 1-11 weeks. The content of styrene in the fat increased linearly during the first 4 weeks and decreased in an exponential manner thereafter. Half of the peak styrene concentration in fat was detected after 9 weeks of exposure.

In 1958, El Masri et al. [210] investigated the metabolism of styrene in rabbits. Hippuric, mandelic, and mercapturic acids, and the glucaronide of phenylglycol were isolated from the urine of rabbits that had been administered styrene orally. The main metabolite (30-40% of the dose) was hippuric acid.

In 1965, Ruvinskaya [211] reported the conversion of styrene to mandelic acid in guinea pigs and rabbits. When guinea pigs were given subcutaneous injections of styrene in sunflower oil (1:1) at 50, 100, or 500 mg styrene/kg, the total mandelic acid found in the urine was 4.0, 7.9, and 36 mg, respectively. At 50 mg styrene/kg, excretion was complete within 1 day; 2 and 3 days were needed to complete excretion of mandelic acid after injection of 100 and 500 mg/kg, respectively. When guinea pigs were exposed to styrene at 1,410 ppm for 5 hours, they excreted mandelic acid for 4 days. The total excreted mandelic acid was 121-157 mg, 80% of which was excreted on the first day.

Ruvinskaya [211] also exposed guinea pigs and rabbits to styrene at 1.2, 12, 235, 705, or 1,175 ppm for 4 hours daily for 3 days. Urine was collected from each animal for 20 hours following each exposure. Mean levels of mandelic acid excreted daily by rabbits exposed at the four highest concentrations were 0.9, 11.2, 26.8, and 40.2 mg, respectively, and, for guinea pigs, they were 1.0, 12.0, 30.1, and 45.5 mg, respectively. There was no elevation of mandelic acid in the urine of rabbits or guinea pigs exposed at 1.2 ppm. When rabbits were exposed at 12 ppm for 4 hours daily for 30 days, mandelic acid excretion was relatively constant at about 1 mg/d. Having assumed a respiratory volume of 500 ml/min and a retention of 50%, Ruvinskaya [211] calculated that about 30% of the absorbed styrene was excreted in the urine as mandelic acid.

In 1971, Bardodej et al. [212] reported on the excretion of styrene metabolites by male Wistar rats exposed to styrene at 446, 728, or 1,856 ppm of styrene vapor for 2-104 hours. Mandelic and phenylglyoxylic acids in the urine were determined by polarography and spectrophotometry. The ratio of mandelic acid to phenylglyoxylic acid averaged 0.61 and ranged from 0.47 to 1.15. There was some indication that the ratios became larger with increasing duration of exposure. Only traces of phenylglycol were found by paper chromatography.

In 1971, Ohtsuji and Ikeda [213] reported studies on the metabolism of styrene (455 mg/kg), styrene oxide (527 mg/kg), phenylglycol (603 mg/kg), phenylglyoxylic acid (500 mg/kg), and mandelic acid (500 mg/kg) in female Wistar rats. Each compound was dissolved in soybean oil, and 2 ml/kg of the mixture was injected ip into rats that weighed about 50 g. Groups of six

rats were studied with each chemical administered. Urine collected from each rat during consecutive 2-hour periods for 10 hours after injection was assayed for glucuronides and hippuric, phenylglyoxylic, and mandelic acids. Some rats were pretreated with phenobarbital twice daily for 4 days before injection to induce hepatic microsomal enzymes; others were treated with a microsomal enzyme inhibitor, 2-diethylaminoethyl-2,2-diphenyl valerate hydrochloride (SKF-525A), before administration of styrene [213].

Injection of styrene and phenylglycol into the rats resulted in increased urinary excretion of a glucuronide (unidentified, but thought by the investigators [213] to be phenylglycol glucuronide) and phenylglyoxylic, mandelic, and hippuric acids. Styrene oxide may have increased glucuronide excretion in the 2 hours after injection; however, the total glucuronide excreted in 10 hours was the same as in controls. Excretion of the acid metabolites was increased after administration of styrene oxide. When phenylglyoxylic acid was injected, it alone was found in large quantities in the urine, indicating that it is an end product of styrene metabolism in the rat. When mandelic acid was injected, phenylglyoxylic, hippuric, and mandelic acids were excreted. When rats were injected with phenobarbital before injection of styrene, the level of styrene metabolites in the urine was increased, but this same effect of phenobarbital was not observed after injection of styrene oxide, phenylglycol, or phenylglyoxylic and mandelic acids [213].

Administration of styrene oxide and phenylglycol resulted in excretion of greater amounts of all the styrene metabolites during the first 2 hours than was observed when styrene was administered [213]. Inhibition of microsomal enzyme activity caused a decrease in the excretion of glucuronide from styrene, but did not affect excretion of the other metabolites. Administration of the microsomal enzyme inhibitor SKF-525A also resulted in a decreased excretion of mandelic acid in the first 2 hours after styrene administration, but no difference in mandelic acid excretion was noted after 10 hours in either the SKF-525A-treated rats or the untreated control rats. Mandelic acid was an apparent precursor of both phenylglyoxylic and hippuric acids. The data are presented in Table IV-24.

TABLE IV-24

EXCRETION OF URINARY METABOLITES 2 AND 10 HOURS AFTER INJECTION OF STYRENE, STYRENE OXIDE, PHENYLGLYCOL, PHENYLGLYOXYLIC ACID (PGA), OR MANDELIC ACID

Substance Injected	Glucuronides mg/kg		PGA mg/kg		Mandelic Acid mg/kg		Hippuric Acid mg/kg	
	2 h	10 h	2 h	10 h	2 h	10 h	2 h	10 h
Saline only	9.2	52.1	0.4	1.8	1.4	7.1	3.2	19.4
Styrene	15.6	70.4	9.1	70.7	11.0	58.8	14.7	78.0
Styrene/PB*	48.1	130.0	39.3	122.6	51.9	131.2	75.7	166.4
Styrene/SKF-525A	8.6	51.5	3.9	54.8	5.1	56.9	5.1	47.0
Styrene oxide	21.8	53.7	14.7	24.1	27.2	45.5	24.9	43.7
Styrene oxide/PB	24.1	59.5	18.7	27.0	31.7	47.6	31.3	52.4
Phenylglycol	41.1	77.4	35.6	89.0	45.4	60.6	75.0	110.0
Phenylglycol/PB	52.5	84.5	41.7	85.5	69.6	85.1	69.3	93.4
PGA	6.7	16.3	38.8	110.4	1.5	8.5	4.0	18.4
PGA/PB	6.9	19.7	47.5	131.7	1.6	9.1	4.2	19.9
Mandelic acid	2.8	16.0	67.9	129.8	110.2	122.1	11.9	35.9
Mandelic acid/PB	3.2	17.6	64.7	136.4	89.3	99.6	11.6	36.9

*PB = Phenobarbital
Use of a slash (/) indicates pretreatment with the substance that follows it.
Taken from Ohtsuji and Ikeda [213]

In 1974, Ikeda et al. [159] found that the 24-hour urinary excretion of mandelic and phenylglyoxylic acids of rats exposed to styrene vapor for 8 hours was linear with styrene exposures up to about 100 ppm, whereas hippuric acid excretion was linear with respect to styrene exposures up to 200 ppm.

In 1978, Seutter-Berlage et al. [214] identified, and determined the molar ratios of, three mercapturic acids that appeared in the urine of adult female Wistar rats after the ip injection of 250 mg styrene/kg once a day, 5 days per week, for 3 weeks. Compounds identified as metabolites of styrene were: N-acetyl-S-(1-phenyl-2-hydroxyethyl) cysteine, N-acetyl-S-(2-phenyl-2-hydroxyethyl) cysteine, and N-acetyl-S-(phenacyl) cysteine. These metabolites were present in a molar ratio of 65:34:1. In a separate

experiment, five rats each received a single ip injection of styrene (250 mg/kg); total mercapturic acids as a percentage of the initial dose were determined to be 10.4% on the first day, and 0.26% on the second day. No mercapturic acids were found on the third day.

Later, in 1980 these same investigators, Delbressine et al. [215] studied whether phenaceturic acid was a urinary metabolite in adult female rats after ip injections of styrene (150 mg/kg) or styrene oxide (150 mg/kg) in sesame oil 5 days per week for 3 weeks. To exclude interference from naturally occurring phenaceturic acid, the experiments were repeated with d8-styrene (styrene with deuterium in the 8 position). After administration of styrene to rats, significantly greater amounts ($p<0.0025$) of phenaceturic acid were isolated from urine during the first 24 hours (as compared with controls) and identified as its methyl ester by thin layer chromatography with the structure confirmed by nuclear magnetic resonance spectroscopy. Quantitative results obtained with gas-liquid chromatography showed 1.4% of a single administered dose to be phenaceturic acid. Neither a single dose nor continuous administration of styrene oxide resulted in any significant increase in urinary phenaceturic acid excretion compared to the control group; the reason for this finding was not clear to the investigators [215]. The studies with d8-labeled styrene and styrene oxide confirmed the findings with the unlabeled substances.

In 1970, Bakke and Scheline [216] studied the metabolism of styrene to phenolic compounds in five male rats. The rats were fed neomycin for 6 days before administration of styrene to inhibit formation of natural phenolic compounds. Styrene, dissolved in 1 ml of propylene glycol, was administered by stomach tube at 100 mg/kg and urine was collected for 48 hours. To convert any metabolites from their conjugated form, the urine samples were treated with an enzyme preparation that contained beta-glucuronidase and sulfatase. During the 48 hours, 0.1% of the initial dose of styrene was recovered as 4-vinylphenol. Other alcoholic metabolites identified were 1-phenylethanol and a trace of 2-phenylethanol. Bakke and Scheline [216] also looked for, but did not find, phenylglycol. Excretion of p-ethylphenol was not greater than control values.

In 1978, Pantarotto et al. [217] administered styrene ip to Sprague-Dawley rats. In addition to phenylethylene glycol and mandelic, benzoic, and hippuric acids, phenolic metabolites, namely, 4-vinylphenol, p-hydroxymandelic acid, p-hydroxybenzoic acid, and p-hydroxyhippuric acid were identified in the urine of the treated animals. These metabolites were characterized by mass spectrometry and by comparative thin layer chromatography with standard compounds. The investigators [217] theorized that the phenolic metabolites could have been formed as a result of chemical rearrangements of unstable arene oxides.

In 1972, Ikeda et al. [218] studied the effects of coadministration of toluene or pretreatment with phenobarbital on the metabolism of styrene in female Wistar rats. Both styrene (228 mg/kg) and toluene (217 mg/kg) were administered ip in soybean oil. Simultaneous administration of toluene

suppressed and delayed the excretion of mandelic and phenylglyoxylic acids, which suggested a competitive inhibition of styrene metabolism by toluene. The observed effect of toluene was attributed to competitive inhibition of the oxidative processes involved in the metabolism of styrene, since phenobarbital pretreatment counteracted this effect [218]. The suppression of oxidation of styrene was a transient effect, since the levels of styrene metabolites in the urine returned to control values 6-8 hours after injection of toluene.

In 1974, Ikeda et al. [159] further studied the metabolism of styrene in rats when styrene was injected ip at doses up to 910 mg/kg into rats and the time course of the urinary excretion of mandelic, phenylglyoxylic, and hippuric acids was monitored. There was a delay in excretion of mandelic and phenylglyoxylic acids; the amounts of these acids excreted were linear with respect to dose only up to styrene doses of 200-250 mg/kg. There were no significant differences between control and styrene-treated animals with respect to urinary hippuric acid excretion at styrene doses below 100 mg/kg. Excretion of hippuric acid became linear with respect to styrene doses above 100 mg/kg [159].

In 1967, James and White [219] studied the formation of mercapturic acids in adult female rabbits and rats treated with styrene and styrene oxide. In one experiment, rats that had been fed yeast containing radioactive sulfur (35S) were given styrene and styrene oxide by stomach tube at doses of about 200 or 250 mg/kg, respectively. Urine was collected over the next 24 hours and assayed for radioactivity. Administration of styrene and styrene oxide resulted in excretion of relatively large amounts of radioactively-labeled hydroxyphenylmercapturic acid, indicating that hydroxylation of the benzene ring of the parent compound had occurred. Traces of labeled phenethylmercapturic acid and an unidentified labeled metabolite were also found.

In another experiment by James and White [219], hydroxyphenylmercapturic acid but no phenethylmercapturic acid was found when unlabeled styrene (145 mg/kg) and styrene oxide (185 mg/kg) were administered by stomach tube to rabbits. No mercapturic acids were found when phenylglycol was given to either rabbits (185 mg/kg) or rats (170 mg/kg). After administration of phenethylmercapturic acid, the rabbits excreted only small amounts of the hydroxy derivative, indicating that another source of this compound was probable. Administration of 8-14C-labeled styrene oxide to rabbits resulted in large amounts of labeled mandelic acid and no naphthoresorcinol-reactive substances. In rabbits, 32% of the administered styrene and 30% of the styrene oxide were converted to mandelic acid. James and White [219] also found that 15-32% of the styrene oxide administered was excreted in rabbits as hippuric acid. With phenylglycol, 17-29% was recovered as mandelic acid, and 4-13% as hippuric acid [219]. No phenolic compounds other than those normally in urine were observed in rabbits given styrene oxide.

In 1977, Vainio and Makinen [220] found that styrene in olive oil, administered ip at 150-1,000 mg/kg, caused a reduction in the hepatic nonprotein sulfhydryl content of female mice, male Wistar rats, female hamsters, and male guinea pigs in about an hour after the injection. Vainio and Makinen [220] suggested that this might reflect the conjugation of reactive alkylating metabolites with hepatic glutathione; they pointed out that the mouse was the most sensitive to this action of styrene, and the rat the least sensitive, possibly because mouse liver has a high epoxide-forming capacity and a low epoxide-inactivating capacity as compared to rat liver.

In 1976, Parkki et al. [221] reported that the activity of epoxide hydratase in Wistar rats increased with increasing styrene doses. Styrene was injected ip in corn oil in daily doses of 100 mg/kg for 3 or 6 days, or 500 mg/kg for 1, 3, or 6 days, or 2,000 mg/kg in one dose. No increases in epoxide hydratase were observed after 3 or 6 doses of 100 mg/kg; statistically significant increases occurred after a single dose of 2,000 mg/kg and 3 or 6 doses of 500 mg/kg. No increase in the activity of uridine diphosphate-glucuronosyltransferase was observed with styrene at any dose, nor was any increase observed in activities of the hydratase or the transferase after one or three doses of styrene oxide (375 mg/kg) or phenylethylene glycol (750 mg/kg).

In 1976, Delag et al. [222] investigated the effect of styrene on carbohydrate metabolism in rats. Glucose, styrene, or glucose and styrene together were administered by stomach tube to two groups of Wistar rats that were either on standard diet or had been food-deprived for 17 hours. Two hours after administration of the compounds, the animals were sacrificed and the left caudate lobe of the liver, the left ventricle of the heart, and the left thigh muscle were removed, homogenized, and assayed for glycogen using anthrone. The results are presented in Table IV-25.

TABLE IV-25

GLUCOSE AND GLYCOGEN IN LIVER AFTER ADMINISTRATION OF GLUCOSE, STYRENE, OR GLUCOSE AND STYRENE TO RATS

Substance(s) Administered	Glucose (mg/g tissue)*		Glycogen (mg/g tissue)*	
	Fed	Fasted	Fed	Fasted
None (control)	5.0	6.3	49.1	13.4
Glucose**	5.6	5.6	39.3	16.6
Styrene**	4.0	5.9	21.2	10.7
Glucose and styrene**	5.9	6.1	33.0	18.2

*Mean of 7 determinations
**Each administered at 2.5g/kg body weight
Taken from Delag et al. [222]

Although styrene caused depletion of hepatic glycogen in both fed and fasted animals, the data [222] indicate that its effect could be reversed by the simultaneous administration of glucose.

In a 1968 abstract, Leibman and Ortiz [223] presented evidence that in the conversion of styrene to phenylethylene glycol in mammalian liver microsomes requiring NADPH and oxygen, styrene oxide was the primary product of the NADPH-dependent oxidation. Mixtures containing styrene, nicotinamide adenine dinucleotide phosphate (NADP), glucose-6-phosphate dehydrogenase, and 9000 x g supernatant fraction of rabbit liver were incubated in air for 5 minutes, and extracted. Styrene oxide was identified either by direct gas chromatography of the extracts or by thin-layer chromatography of the picric derivative. No styrene oxide was found when NADP and glucose-6-phosphate dehydrogenase were omitted. When 8-14C styrene was incubated in the above system with a pool of unlabeled styrene oxide, about equal radioactivity was found in the phenylethylene glycol and in the picric derivative of styrene epoxide.

Later, in 1969, Leibman and Ortiz [224] demonstrated the in vitro formation of phenylglycol from styrene by hepatic microsomal preparations in rats and rabbits pretreated with phenobarbital. Ethyl acetate extracts of a reaction mixture that contained 50 µmol of styrene in 0.5 ml of dimethylformamide were qualitatively analyzed by gas chromatography. Peaks having the same retention times as a reference standard of phenylglycol appeared following incubation. In addition, thin layer chromatography of the ethyl acetate extracts after both acetylation and trimethylsilylation yielded areas having the same reference values in three different solvent systems as the acetylated and silylated derivatives of standard phenylglycol [224].

In 1970, this work was further extended by Leibman and Ortiz [225] to demonstrate that styrene oxide may be an intermediate in the formation of phenylglycol. Styrene oxide was identified in ethyl acetate extracts of rabbit liver microsomal preparations that had been incubated with unlabeled styrene and styrene labeled with carbon-14 at the 8 position. The oxide intermediate was demonstrated by three methods: gas-liquid chromatography, thin layer chromatography, and by accumulation of radioactivity in a pool of styrene oxide added to reduce the effect of epoxide hydratase.

In 1976, Salmona et al. [226] studied the enzymatic capacity for epoxidation in the liver, lungs, kidneys, heart, spleen, and brain of male and female rats. Microsomes from the organs were incubated with styrene or styrene oxide, and the activities of monooxygenase and of epoxide hydratase were assayed. The investigators [226] found that styrene oxide formation, i.e., monooxygenase activity, is dependent on the availability of NADPH. Inhibitors of cytochrome P-450 (metyrapone and SKF-525A) and inhibitors of epoxide hydratase (cyclohexene oxide and epoxytrichloropropene) were studied for their effect on enzyme activity of hepatic microsomes. The cytochrome P450 inhibitors significantly inhibited ($p<0.01$) both styrene monooxygenase

and epoxide hydratase activities. The epoxide hydratase inhibitors markedly inhibited epoxide hydratase but not monooxygenase activity.

In 1978, Cantoni et al. [227] studied the activities of styrene monooxygenase and epoxide hydratase in rats, mice, guinea pigs, and rabbits of each sex and found the highest activity of each enzyme in the liver, with the hydratase activity being higher than that of monooxygenase. Each enzyme was also found in microsomal fractions from the heart, lungs, spleen, and kidneys. Styrene or styrene oxide was the substrate used in incubating the microsomal preparations prior to enzyme assay. Because of the high ratio of hydratase to oxygenase activity in the rat, Cantoni et al. [227] suggested that the rat would be relatively resistant to styrene toxicity, assuming that oxygenase caused styrene oxide to form and that hydratase (as well as glutathione-S-transferase) inactivated the styrene oxide. Because of the low activity of epoxide hydratase in mouse and rabbit lungs in comparison to activating capacity, the investigators [227] speculated that the lungs of these two species would be the most sensitive site for styrene toxicity.

Because of the work of Bakke and Scheline [216], who found 4-vinylphenol in the urine of rats given large amounts of styrene, Watabe et al. [180] suggested in 1978 that 1-vinylbenzene-3,4-oxide (styrene-3,4-oxide) might be the precursor of both 4-vinylphenol and 1,2-dihydroxy-1,2-dihydro-4-vinylbenzene, and that an oxygenated metabolite of the latter compound is a proximate mutagen. In another 1978 investigation, Watabe et al. [228] incubated rat liver microsomes with styrene, and identified styrene oxide (or at least a chromatographic peak with the same retention time as styrene oxide). Maximal amounts of the oxide were found after an incubation period of 10 minutes, thereafter decreasing so that at 40 minutes the oxide was not detectable. Styrene glycol was formed in increasing amounts until a maximum was reached at 60 minutes.

In 1981, Belvedere and Tursi [229] studied the oxidation of styrene to styrene oxide in human blood erythrocyte and lymphocyte suspensions. Styrene oxide formed enzymatically was quantitatively hydrated by acidification to styrene glycol, a compound more suitable for gas chromatographic analysis. Styrene oxidation in human erythrocytes was inhibited by carbon monoxide, occurred in the absence of NADPH and NADP, and was undetectable in the absence of oxygen. The finding that oxygen was required to catalyze the formation of styrene glycol is indicative that the glycol was in fact formed from styrene oxide and not directly by the hydration of styrene. Lymphocytes (with the addition of NADPH and NADP) were more active than red blood cells in styrene oxidation.

However, in 1982, Beije and Jenssen [230] conducted a mutagenicity study with an isolated perfused rat liver as a metabolizing system and Chinese hamster V79 cells as genetic target cells. Styrene oxide was rapidly metabolized by the perfused liver, and thus, no mutagenic effect was detected. However, when styrene was added to the perfusion system, an increase in mutations in the V79 cells were observed regardless of where in

the circulation perfusion medium the V79 cells were placed. The mutagenicity of styrene was five times higher as compared to using an S9 mix from the same rat strain as the metabolizing system. The simultaneous analysis of styrene oxide in the perfusion medium indicated concentrations only 2-4% of the original amount of styrene. Beije and Jenssen [230] suggested that their results using the liver perfusion/cell culture system mimics the metabolism expected to be found in the intact animal, thus indicating that styrene oxide is not the principal mutagenic metabolite of styrene *in vivo*.

In 1977, Ryan and Bend [231] demonstrated that biliary excretion of the glutathione conjugate was dose-dependent with respect to styrene oxide in perfused rat liver preparations. In 1977, additional work with styrene oxide was reported by Bend et al. [232] who perfused rat livers *in vivo* by cannulation of the portal vein, the thoracic vena cava, and the bile duct. Using styrene oxide at 0-500 µmol per liver, they found labeled 8-14C styrene oxide bound to DNA, RNA, and protein, even when the organ was challenged with only 1 µmol of styrene oxide. The binding increased with increasing styrene oxide concentrations, and at 500 µmol a marked increase in its binding to protein was observed simultaneously with microscopic changes of the liver and depletion of hepatic glutathione [232].

SUMMARY

A summary of information on possible effects of styrene on health follows.

Effects on the Nervous System

Experimental exposures in humans to styrene have demonstrated that styrene causes CNS depression [68,69,70,71,72]. Within minutes of an exposure at 800 ppm, 2 men experienced listlessness, drowsiness, and impaired balance [68]. During a 1-hour exposure to 376 ppm, decrements in balance, coordination, and manual dexterity tests were measured, and subjective complaints of headache, nausea, and a feeling of slight inebriation were reported [69]. A significant difference in reaction time was noted in 12 subjects after a 2-hour exposure that included consecutive 30-minute styrene exposures of 50, 150, 250, and 350 ppm [71]. Slower reaction times were found in 2 or 3 subjects during 90-minute exposures of 50, 100, and 200 ppm; loss of balance was found for 3 subjects during the 90-minute exposure at 200 ppm [72]. Subjective complaints reported by 6 subjects during 90-minute styrene exposures at 50, 100, or 200 ppm included headache, fatigue, sleepiness, malaise, difficulty in concentrating, and a feeling of intoxication [72]. During the course of a study lasting a couple of weeks, which included a series of styrene exposures at 20, 100, and 125 ppm for 7.5 hours, there were some changes in 3 of 6 subjects in both visual

evoked response and EEG amplitude, which the investigators [70] deemed to be consistent with CNS depression.

However, there have also been experimental studies showing styrene to have little effect on the central nervous system. After experimental styrene exposures of 50 ppm for 1 hour, 99 ppm for 7 hours, 117 ppm for 2 hours, or 216 ppm for 1 hour, no significant CNS effects (e.g., decrements in balance, coordination, and manual dexterity) were noted [69]. No changes in manual dexterity or perceptual tests were noted after consecutive 30-minute exposures to 50, 150, 250, and 350 ppm [71]. Loss of balance was not found during 90-minute exposures to 50 or 100 ppm [72]. In exposures for 1, 3, or 7.5 hours to 20, 100, or 125 ppm of styrene, no deleterious effects on equilibrium, cognitive testing scores, or EMGs were found [70]. No significant optokinetic changes were noted in 5 subjects exposed to 300 ppm of styrene for 1 hour [73].

Workers exposed to styrene have experienced weakness [105], increased reaction times [111,392], abnormal EEGs [63,106,108,118,124,125], and headache, fatigue, malaise, tension, or dizziness [59,63,67,82,84,94,101,102, 105,106,108,109,110,112,113,123,138]. Styrene exposures in many of these studies were either not determined [63,67,101,108], or were at times greater than 100 ppm for some of the workers [59,102,105,106,111,112,113,123,138]. However, at one RP/C facility where the average styrene exposure was estimated from urinary mandelic acid measurements to be about 30 ppm, 24% of the workers had EEGs judged to be abnormal [124].

There is some evidence of styrene-induced peripheral neuropathy. In an investigation of workers at a U.S. styrene and polystyrene production plant (with potential exposures to styrene, benzene, ethylbenzene, and toluene), radial and peroneal nerve conduction velocities were said to be reduced, but comparative data on normal velocities were not given [81]. It was also reported in the same study [81] that radial and peroneal nerve conduction velocities decreased with increasing duration of exposure, but because appropriate corrections for age were not made, it is not evident whether the decrement with longer exposure was due to the longer exposure, increasing age, or a combination of both. In a Swedish study [123], 10 of 33 workers exposed to about 5-125 ppm of styrene had evidence of a mild sensory neuropathy with polyphasic sensory responses; these 10 workers were older than those not having signs of neuropathy, and they were more heavily exposed. The investigators [123] speculated that age alone did not cause these effects, but that the effects of age and styrene exposure might have been synergistic. It seems evident that more investigation of nervous system effects is needed.

Irritant Effects

Irritation of the eyes has occurred in human subjects undergoing single exposures [68,69,70,72] and in workers during repeated exposures

[35,53,58,61,104,110,113,126] to styrene. Styrene has also been reported to cause superficial transient burns of the human cornea [55]. Irritation of the respiratory tract has occurred in human subjects [68,69,70,72] and in workers [35,53,59,56,93,104,113,123,126] exposed to styrene. As would be expected since styrene is a defatting agent, styrene is a primary skin irritant [234], and has caused dermatitis, including a rash and chapped skin in workers [54,56,61,91,104,113,122,126].

Volunteer subjects exposed to styrene vapor at 800 ppm had immediate eye, nose, and throat irritation [68]. At 376, 216, and 99 ppm, human subjects developed eye or respiratory tract irritation within 20 minutes of the start of exposure [69]. In another experimental study [70], the incidence of eye, nose, and throat irritation for male subjects was 13% at 0 ppm, 17% at 20 ppm, 20% at 100 ppm, 33% during exposures fluctuating between 75 and 125 ppm, and 45% at 125 ppm styrene; the incidence of eye, nose, and throat irritation for female subjects was 8% at 0 ppm and 32% at 100 ppm. Irritation of the eyes was noted by volunteer subjects in another study [72] during styrene exposures of 50, 100, 200, and 300 ppm.

Workers exposed to styrene in reinforced plastics applications complained of eye and respiratory tract irritation, but were able to tolerate styrene exposures in excess of 500 ppm for several hours at a time [35]. Among 35 reinforced plastics workers exposed to styrene at 44-550 ppm, 34 complained of some sort of eye, nose, or throat irritation; and about half of them complained of wheezing, shortness of breath, or chest tightness [104]; exposure to an isocyanate (MDI) might have contributed to some of these effects. Complaints of wheezing and chest tightness have also been noted in workers during an investigation of a styrene and polystyrene production plant [82]; however, spirometric studies of airway effects did not suggest significant changes, nor was there any radiologic evidence of significant lung change observed. In a factory where reinforced plastics were made, workers exposed to TWA styrene concentrations of 9-111 ppm (average 69 ppm) complained of chest tightness (23% of the workers), wheezing (18%), and shortness of breath (54%), but ventilatory function was significantly changed during the shift only in those workers that smoked [113]. Among 21 workers exposed to styrene at about 75 ppm for about 10 years at another RP/C plant [114], there were four cases of reduced FEV_1, but whether the cause was age, styrene exposure, or other factors was not clear. As compared to controls, a significantly greater number of RP/C workers in another clinical study had abnormal pulmonary function [91].

Irritation of the eyes and upper respiratory tract has occurred in some workers and experimental subjects at styrene concentrations well below 200 ppm. More research into long-term respiratory effects of styrene is needed.

Effects Involving the Liver

Various clinical studies [82,96,103,113,115,116,120] have suggested that styrene exposure has affected liver function, based on several tests. Among the findings, which may indicate liver function changes, were elevated serum enzyme activities [82,96,103], elevated serum uric acid [113], increased glucose tolerance [115,116,120], and a low glucose assimilation coefficient [116]. In one study designed to investigate liver function among polystyrene production workers, the authors [96] concluded that styrene exposure caused hepatic dysfunction reflecting metabolic disturbances, but not of a pathological degree.

A clear-cut trend toward altered liver function has not been demonstrated. In addition, the more commonly used tests such as changes in serum enzyme levels of hepatic origin were not always used. Animal studies [53] have suggested that styrene is hepatotoxic only at concentrations much higher than those found in the workplace. Damage to the hepatic parenchyma of rats after a single exposure to styrene vapor at 2,500 ppm for up to 21 hours was reported by one group of investigators [53], who also reported increases in the liver weights of rats repeatedly exposed to styrene vapor at 1,300 ppm for 130-139 days. However, they found no liver damage in guinea pigs exposed at 650 ppm or rabbits and monkeys exposed at 1,300 ppm for similar periods. Another group [169] noted parenchymal alterations and congestion in the liver of rats intermittently exposed for 2 weeks to 300 ppm of styrene 6 hours per day, 5 days per week. Research to clarify the role of styrene on liver status is needed. Meanwhile, for worker protection, liver function should be periodically assessed due to the importance of this organ in the biotransformation and detoxification of toxic substances.

Mutagenicity

Many *in vitro* tests of mutagenicity have indicated that styrene has no mutagenic activity. This has been found with *S. typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 [172,173,174,176] as well as with *E. coli* K12 [174], the yeasts *S. pombe* and *S. cerevisiae* [175], and cultured Chinese hamster V79 cells [175,176]. However, a few studies [171,177,178] have found weak evidence of the mutagenicity of styrene in *S. typhimurium* strains TA 98 and TA 1538. Styrene oxide has been shown to be mutagenic toward *S. typhimurium* TA 100 and TA 1535 [171,172,173,174,176,178], *E. coli* K12 [174], the yeasts *S. pombe* and *S. cerevisiae* [175], and Chinese hamster V79 cells [175].

There was increased uptake of tritiated thymidine into the DNA of heteroploid human cells, reflecting unscheduled DNA synthesis, following treatment with styrene oxide but not with styrene [176]. Chromosomes from human lymphocytes incubated with styrene or styrene oxide had more abnormalities than controls, though the abnormalities in chromosomes in styrene-treated cells were different from those in the styrene oxide-treated

cells [179]. Doubts about the applicability of this *in vitro* test are amplified by the suggestion of the investigators [179] that impurities in the styrene preparation might have been responsible for the effects. However, a later study by the same group [181] showed a clear dose-response relationship in the induction of sister chromatid exchanges (SCE) in human whole blood lymphocyte cultures treated with styrene.

In vivo tests have also given conflicting results. In a host-mediated assay [175], a high dose of styrene (i.e., 1 g/kg) produced gene conversions in the yeast *S. cerevisiae* which had been injected ip into mice. Mice intubated with styrene oxide, but not those intubated with styrene, had a significantly elevated incidence of chromosomal aberrations in bone marrow cells removed 24 hours after administration of the dose [176]. An increase in the frequency of SCE in alveolar macrophages, in bone marrow cells, and in regenerating liver cells was observed in mice exposed to styrene at 565 ppm for 6 hours per day for 4 days [183]. Chromosomal breaks were also found in the bone marrow of rats exposed to styrene vapor [184], but not in mice [176] or hamsters [185]. Styrene has also caused recessive lethal mutations in fruit flies [187].

Chromosomal changes were found to be more frequent in the lymphocytes of styrene-exposed workers in several European RP/C factories than among controls [76,129,130,131,132]. An increased frequency of SCE in the lymphocytes of styrene-exposed workers has also been reported [132]. However, other studies of workers exposed to styrene have shown no significant increases in either chromosomal aberrations [134,136] or SCE [136]. In a study of unscheduled DNA synthesis in lymphocytes of styrene-exposed workers, styrene did not alter the efficiency of DNA repair, but rather predisposed the lymphocytes to an increased risk for DNA damage from subsequent exposures to genotoxic agents [137].

The reasons for the different results in the many tests of mutagenicity of styrene are not known, so a conclusion on whether styrene is a mutagen seems premature. It may be that these different results reflect the different capabilities or efficiencies of metabolism by the various species or mutagen assay systems; for example, if one species hydrates styrene epoxide as soon as it is formed, styrene should be less potent, or even inactive, as a mutagen than in another species lacking the ability to inactivate the epoxide so rapidly. (This argument is based on the reasonable although unproved premise that styrene epoxide formation is the basis for any mutations.)

Reproductive Effects

Congenital defects in children whose mothers had been occupationally exposed to styrene were reported by Holmberg [66]; a more thorough investigation is needed to verify the implications of these findings. The finding of styrene, at unstated concentrations, in umbilical cord blood [65] suggests that styrene can cross the placenta; in these cases, the

source of the styrene exposure of the mothers was not found. Placental transfer of styrene in rats has also been noted [189]. An increased rate of spontaneous abortions observed among Finnish styrene workers [139] might be compatible with findings of cytogenetic effects or of terata; thus, despite lack of confirmation of this study, the finding warrants concern. A later study, however, found no difference in the number of spontaneous abortions between styrene workers and a group of age- and social class-matched controls with no solvent exposures [140].

Ragul'ye [190] found an increased incidence of pre-implantation loss and total embryo mortality in female rats that had been exposed to styrene at 12 ppm for 4 hours per day throughout gestation. The study by Vergiyeva et al. [191], conducted like that of Ragul'ye [190] but involving a higher styrene exposure concentration of 47 ppm, found no significant evidence of embryotoxicity, thereby refuting the Ragul'ye study. Murray et al. [192] investigated teratogenicity in rats and rabbits exposed to styrene by inhalation of vapor or by intubation of liquid and found no significant evidence that styrene is teratogenic; however, the dams were not exposed during the first or last trimester of gestation. None of these three investigations [190,191,192] found evidence of teratogenicity. Similarly, Kankaanpaa et al. [193] did not find a significant excess of malformed fetuses from mice and hamsters exposed to styrene vapor; however, fetotoxicity (an excess of dead or resorbed fetuses) was found from hamsters exposed on days 6-18 of pregnancy at 1,000 ppm styrene, but not at lower concentrations. Ponomarkov and Tomatis [196] found a significantly greater pre-weaning mortality of progeny of female 020 mice administered a single 1,350 mg styrene/kg dose by stomach tube on day 17 of gestation; significant results were not found in similar experiments with C57 Bl mice or BD IV rats. A study [170] sponsored by the Chemical Manufacturers Association concluded that styrene administered in the drinking water had no deleterious effects on the reproductive capacity of rats through three generations.

In summary, styrene does not appear to be teratogenic, embryotoxic, or fetotoxic but further investigations of the reproductive outcomes of workers exposed to styrene are needed.

Carcinogenicity

The possible carcinogenicity of styrene has been investigated by long-term administration to rodents [195,196,197,198]. One of these investigations [195] involved vapor exposure. That study, which used rats, resulted in an increase in the combined incidence of leukemia and lymphosarcoma in female rats only that was not statistically significant. There was a high incidence of intercurrent disease (i.e., chronic murine pneumonia) in the male rats such that conclusions from the investigation are inappropriate. In another study [196], styrene was administered in olive oil by stomach tube to one strain of rats and two strains of mice. There was a statistically significant increase in lung adenomas and adenocarcinomas only in female mice of one strain; the authors [196]

suggested that their data provided weak evidence of the carcinogenicity of styrene. An NCI investigation [197] also developed equivocal evidence. There was a significant increase in lung adenomas and adenocarcinomas in male mice (when compared with matched controls but not when compared with historical controls), but not in female mice or rats. NCI [197] concluded that the data provided "suggestive" but not "convincing" evidence of the carcinogenicity of styrene, and recommended another experiment to help resolve the point. A companion experiment [198], involving the administration of a mixture of styrene and beta-nitrostyrene, also gave equivocal results.

Mortality studies of workers exposed to styrene have not shown an excess cancer mortality [31,78,83,84,142]. There have, however, been suggestions of an excess of leukemia. Nicholson et al. [83] studied the mortality experience in one U.S. styrene and polystyrene production plant, and found 83 total deaths vs. 106 expected among those exposed 5 years or more. There was no excess of deaths from cancer or from any of the nonneoplastic diseases examined such as cardiovascular or respiratory disease. The investigators [83] anticipated an excess of leukemia because of previous exposure of many of these workers to benzene; they found two cases of leukemia and one of lymphoma in the study group. They examined 361 death certificates of other workers employed at least 6 months at the plant and five additional cases of leukemia and four of lymphoma were found. The investigators [83] concluded that the information found regarding leukemia was not definitive.

In a U.S. styrene production plant, Ott et al. [31] found fewer total deaths (303 vs. 425) and fewer cancer deaths (58 vs. 76.5) among 2,904 workers at four plants than would be expected from the U.S. white male population. Most of these workers had been exposed to low levels of styrene during their employment (TWA concentrations were 10 ppm or less). The mortality data on the styrene workers (i.e., production and non-professional research) was also compared with previous mortality experiences from that company, and the styrene workers had a lower total mortality and a lower cancer mortality. However, there was a significant excess ($p<0.05$) of leukemia deaths compared with other company workers (6 observed vs. 1.6 expected), although the excess was not significant when compared with the U.S. population (6 vs. 2.9). Most of the excess was due to lymphatic leukemia. Some workers had been exposed many years earlier to high levels of benzene, but whether those men with leukemia had been exposed to benzene was not evident.

No excess of cancer was seen in a German styrene and polystyrene plant [78]. In that study, 74 death certificates were examined, and there were 12 deaths from cancer, 3 of them from lung cancer, neither significantly different from the comparison groups.

In a study of 1,205 reinforced plastics workers in Sweden [142], where exposure levels were thought to be 150-300 ppm styrene in recent years and higher in the past, a slight but nonsignificant decrement in cancer

incidence from that expected in the Swedish population was found. The latency period was not high for many of the workers, so further followup might reveal more cases of cancer.

From the experimental animal investigations and from the epidemiological studies, there seems little basis to conclude that styrene is carcinogenic. If styrene oxide is an intermediate metabolite, covalent binding to nucleic acids leading to cancer development might be predicted; however, there is little evidence that this epoxide is formed in vivo. Nonetheless, the enzyme catalyzing the formation of this epoxide from carbon-carbon double bonds exists in many tissues, as do the enzymes catalyzing the hydration or other inactivation of the epoxide. If these enzymes are in the same cells, it may be that the epoxide is formed and then rapidly deactivated; if it exists long enough, it might be carcinogenic. This speculation, if valid, could suggest that styrene is a weak carcinogen. Examination of the ratios of these enzymes in various tissues of several animal species [220,227] suggests that the mouse should be one of the more sensitive species. Two studies of experimental carcinogenesis [196,197] found positive results only in mice, a point compatible with the speculation, even if not proving it. Suspicions that the epoxide may be stable long enough to react with other molecules before being inactivated are enhanced by evidence [235] that the cytochrome P-450 monooxygenase system is not close, in a spatial sense, to epoxide hydratase and to transferases in the endoplasmic reticulum.

Thus, while it does not seem appropriate from presently available evidence to conclude that styrene can cause cancer among exposed workers, there is enough reason to suggest it might be at least a weak carcinogen, and priority should be given to further studies of this problem.

While several experimental tests of the carcinogenicity of styrene oxide have been inconclusive [199,200,201], an investigation in Italy [202] developed persuasive evidence that styrene oxide can cause stomach tumors in rats administered the compound by intragastric catheter. It seems reasonable to predict that administration of this compound by inhalation could cause tumors of the respiratory tract, and that styrene oxide could cause cancer in humans.

Uptake, Metabolism, and Elimination

Liquid styrene is readily absorbed through intact skin of man [151] and of animals [165]. Moreover, styrene vapor can penetrate the skin of man [154], although less efficiently than the liquid. Styrene is also retained after inhalation of the vapor, with retention rates reported to vary from 60 to 75% [69,88,143,146].

Absorbed styrene is eliminated from humans mostly in the urine as metabolites, but some excretion of unchanged styrene from the lungs occurs [91]. Metabolites reported in human urine include mandelic acid [35,72,88, 109,125,144,151,159], phenylglyoxylic acid [35,144,159], and, at higher

doses, hippuric acid [68,159]. These are also the most commonly found metabolites in the urine of styrene-treated experimental animals [53,206,207, 210,211,212,213,217,219], but other metabolites have also been found, namely, mercapturic acids [53,210,214,219], benzoic acid [206,207,217], 4-vinylphenol [216,217], 2-phenylethanol [216], phenaceturic acid [215], and phenylglycol [210,212], some of which may be excreted as conjugates of glucuronic acid or glutathione [68,203,210,213].

Styrene oxide, also known as styrene epoxide, has been proposed [224,225] as an intermediate in the metabolism of styrene, but it has not been found *in vivo*. However, phenobarbital-activated rat microsomes converted styrene to the epoxide [224] as determined by an indirect method.

An epoxide-forming enzyme (monooxygenase) has been found in a number of tissues of mice, rats, guinea pigs, and rabbits [226,227], but an epoxide inactivating enzyme (glutathione-S-transferase or epoxide hydratase) was also present in these same tissues. Thus, it seems possible that styrene is converted to styrene epoxide and is then further converted to such final products as mandelic and phenylglyoxylic acids. Whether styrene oxide (if formed) is present long enough to bind covalently to genetic material or other macro molecules is not known; from indirect evidence, styrene's lack of potency in causing mutations or tumors suggests that styrene oxide, if formed, is present only briefly.

This ability of epoxides to alkylate or arylate nucleic acid, thereby presumably leading to germinal or somatic mutations, is the major concern in the question of intermediary metabolism of styrene.

Other Effects

Other effects reported among styrene-exposed persons include gastralgia and nausea [72,101,102,104,109,110], nose bleed [93,104,105], blood dyscrasias [102], lowered arterial blood pressure [94], elevated blood pressure [105], enlarged thyroid [113], retrobulbar neuritis [57], thrombosis of the central retinal vein [62], gall bladder inflammation [74,105], decreased vision [59], decreased alcohol tolerance [128], abnormal thyroid size [113], and psychasthenia [64]. It does not seem appropriate to attribute these to styrene absorption (except perhaps for the gastrointestinal effects) on the basis of these few, unconfirmed observations.

Conclusion

Styrene is readily absorbed by the respiratory and gastrointestinal systems, and the skin. Exposures to styrene have caused CNS depression; subjective complaints included headache, fatigue, sleepiness, nausea, malaise, difficulty in concentrating, and a feeling of intoxication.

Decrements in balance, coordination, and manual dexterity tests have also been reported, as have slower reaction times and abnormal EEGs. Styrene vapor is also an irritant to the eyes and upper respiratory system, and liquid styrene is a skin irritant. Various clinical studies have suggested that styrene exposure has affected liver function.

Limited human data suggest that styrene might be teratogenic, but several studies with experimental animals indicate that it is not. Most, but not all, *in vitro* studies suggest that styrene is not mutagenic, but some mammalian studies, including observations of several groups of styrene workers, suggest cytogenetic changes may result from working with styrene. An increased rate of spontaneous abortions was observed in one group of RP/C workers, but not in another group. Styrene has been associated with an increase in lung tumors (although not consistently among species) in two experimental animal studies, while another study showed an elevation, though not statistically significant, in the combined incidence of leukemia and lymphosarcoma in female rats. Mortality studies of styrene workers have shown no excesses in overall cancer incidence. However, excesses of deaths, though not statistically significant, have been reported in the specific cancer categories "Lymphatic and Hematopoietic, except Leukemia" and "Leukemia."

Most of the styrene absorbed by humans is excreted in the urine as mandelic and phenylglyoxylic acids, and the urinary concentrations of the two or of just mandelic acid reflect amounts of styrene absorbed through the respiratory tract and through the skin (as well as through the gastrointestinal tract, if poor hygiene and work practices allow ingestion).

V. RECOGNITION OF THE HAZARD

Environmental Sampling and Analytical Methods

The following discussion about the methods of sampling and analysis of styrene briefly describes various methods that have been used or proposed. While the recommended methods of sampling and analysis will usually be the most useful, local factors, e.g., availability of equipment, knowledge of usual concentrations, confounding variables, exposure patterns, etc. may make another method desirable.

(a) Sampling Methods

(1) Absorption Methods

Airborne styrene has been absorbed into liquids in glass impingers or bubblers. The liquid may be inert to styrene [35,236,237,238,239, 240], may react, or may contain solutes that react with styrene to form suitable derivatives [241,242,243,244]. Cooling has sometimes been employed to minimize evaporation losses and increase trapping efficiency [98,107,236,238,242]. Liquids that have been used to collect styrene from air include ethanol [35,236,237,241,245], isopropanol [107], methanol [98], glacial acetic acid [238], isooctane [240], concentrated sulfuric acid [246], dilute sulfuric acid [243], cold carbon tetrachloride [98], and nitric acid in sulfuric acid [242,244]. Some of these liquids are corrosive or otherwise toxic, so their use in a manner that might result in contact with workers (e.g., from broken impingers) is undesirable. Also, liquid impingers should be avoided when possible because they may impose restrictions on a worker's activities to avoid spillage.

(2) Adsorption Methods

Styrene has been adsorbed onto the surface of solid sorbents such as silica gel [107,238,245,247,248], porous polymers [249,250], and activated carbon [249,251,252,253,254,255,256,257].

In 1965, silica gel, as a collection medium for styrene, was evaluated by Van Mourik [107] during industrial hygiene surveys. By collecting duplicate field samples over a 4-year period at airborne styrene concentrations averaging 20 ppm, Van Mourik [107] found that the relative standard deviation of duplicate samples was 4.6%. Styrene was desorbed by isopropyl alcohol. To investigate the stability of adsorbed styrene, duplicate samples were collected in midget impingers containing isopropyl alcohol; results with silica gel were always higher. Van Mourik [107] concluded that silica gel collected styrene efficiently and that the adsorbed styrene was stable. In 1966, Campbell and Ide [245] obtained comparable recoveries of styrene from both silica gel and an ethanol bubbler over the range of 10-200 ppm.

Styrene adsorbed on porous polymers or charcoal can be removed by heating [249] and can be conveyed directly into a gas chromatograph, thereby avoiding dilution of styrene with a solvent. In 1976, Parkes et al. [249] found a relative standard deviation of 4.3% from the analysis of samples collected from air containing 11.8 ppm of styrene; the total amount of styrene collected was 5 µg. By removing styrene from activated charcoal with heat, they found a lower detection limit of 0.2 ppb in 10-liter air samples. Extrapolating this detection limit to styrene dissolved in 1 ml of carbon disulfide, Parkes et al. [249] estimated that the detection limit of styrene would be 40 ppb in a 10-liter air sample. This estimate does not consider possible problems that may be associated with recovery and solvent interference. A disadvantage of using thermal desorption is that the entire sample is usually used for a single analysis.

Charcoal as a collection media for styrene has been extensively studied [249,251,252,253,254,255,256,257,258,259]. In an initial study in 1966, Fraust and Hermann [251] obtained five replicate samples from air containing 100 ppm of styrene by sampling for 10 minutes at 200 ml/min. Each sample was analyzed in triplicate and a relative standard deviation of 7% was found. The investigators [251] found that when an atmosphere containing 100 ppm of styrene was sampled at 1 liter/min, the collection efficiency was 85%, but when the same atmosphere was sampled at 100 ml/min, the collection efficiency was only 30%. This rather unexpected variation in sampling efficiency with respect to sampling rate has not been confirmed by other investigators.

In 1978, using four charcoal tubes in series, each tube containing 350 mg of charcoal, and by sampling at 200 ml/min, Severs et al. [252] recovered 93-100% of styrene under varying relative humidities (23-80%), sample volumes (70-95 liters), and styrene concentrations (0.4-14 ppm). The smallest quantity of styrene collected during this study [252] was equivalent to sampling 10 liters of air at 4 ppm. This study demonstrates that styrene can be recovered in high yields from charcoal tubes if breakthrough can be avoided, indicating that desorption efficiency is adequate.

In 1977, Saalwaechter et al. [258] also studied styrene stability on charcoal tubes under varying conditions: temperature (-13 to 48°C), storage time (1-80 days), and light (19 days of sunlight, light from a sun lamp for 24 hours, or no light). The investigators [258] concluded that the stability of styrene on charcoal was not affected by temperature, light, or storage time. From their studies of the effect of humidity (7-94%) on the adsorption of toluene onto charcoal, it was inferred that high humidity may also adversely affect the adsorption of styrene onto charcoal. Saalwaechter et al. [258] also found that the efficiencies of desorbing styrene from charcoal with carbon disulfide were equivalent (85-89%) for charcoal obtained from three different manufacturers. Using an air flow of 1 liter/min, a relative humidity of 7%, and a styrene concentration of about 150 ppm, 1% breakthrough for the 100 mg front section occurred at 29.1 liters, at which time the front section of the charcoal tube held 18 mg of styrene.

Tubes containing charcoal have been designed for use in industrial hygiene surveys and are commercially available [253]. Such tubes were evaluated in 1976 by Burnett [253] at 50, 100, and 200 ppm of styrene by sampling these atmospheres at 1 liter/min. The mean percent recovery of styrene was 85%. These tubes contained two sections of charcoal; the main collecting section had 100 mg, and the reserve (backup) section, 50 mg.

In 1975, using tubes containing 200 mg of charcoal, Kalliokoski and Pfaffli [254] found that charcoal could collect 70 mg of styrene by sampling at 0.2-0.3 liters/min from a chamber containing 1,120 ppm of styrene. With charcoal tubes loaded with up to 66 mg of styrene, about 95% of the styrene remained on the charcoal after drawing fresh air through the tubes at this flow rate for 3 hours. Styrene was desorbed from the charcoal with dimethyl formamide; the desorption efficiency was 72.3%.

In 1972, after sampling air that contained 49, 494, or 987 ppm of styrene through 200-225 mg of charcoal at 0.2 liters/min for 1 hour, Gotell et al. [35] recovered 96%, 90%, and 87% of the styrene, respectively. Carbon disulfide was used to desorb styrene from the charcoal.

In 1977, NIOSH contractors evaluated data on the collection of styrene by charcoal tubes at 100, 200, and 400 ppm by sampling at 0.2 liters/min for 25 minutes [255]. Desorption efficiencies of 87% at 100 ppm, 88% at 200 ppm, and 93% at 400 ppm were found when carbon disulfide was used to desorb the styrene. At 400 ppm, sampling continued for 111 minutes before a significant amount of styrene (5%) passed through the charcoal, which then contained 36 mg of styrene.

Although the report by Fraust and Hermann [251] indicated that the collection efficiency of charcoal tubes was affected by the sampling rate, data from other studies [252,253,254,255,258] indicate satisfactory collection of styrene at all sampling rates studied. Passive dosimeters, which collect organic vapors through the mechanism of molecular diffusion and adsorption onto charcoal can also be used for monitoring styrene exposures [257].

(3) Cryogenic Methods

In 1967, Klyuzko and Vovyanko [247] used a liquid oxygen trap for sample collection to study styrene and ethylbenzene air pollution caused by the polystyrene industry. The frozen compounds were released directly into a gas chromatograph by heating the trap. This method, also discussed by Parkes et al. [249], did not seem to offer any advantages over other methods of collection for industrial hygiene use, but did create a potential hazard in the transport and use of liquid oxygen.

(4) Methods of Collecting Total Air Samples

The methods discussed above concentrate and remove styrene from air. Total air samples collected in syringes, pipets, bottles, or plastic

bags for analysis by a variety of methods do not concentrate styrene; these methods [69,243,260,261,262] usually sample small volumes of air over short periods of time. Because of the small sampling volumes and short sampling times, such samples may be better able to reflect periodic fluctuations in styrene concentrations than are samples collected by absorption, adsorption, or cryogenic methods. This may be desirable if the sampling times are carefully chosen [263]. Under certain conditions, however, glass surfaces may adsorb styrene [264] and some plastic bags are permeable to styrene [265]. Thus, care must be taken to ensure that all the styrene has been recovered from the collection device. This, however, may not be a problem below 100 ppm of styrene. In 1974, De Gesero [32] reported that styrene concentrations in air samples collected in plastic bags were stable for 4 hours. However, in 1978, Severs et al. [252] found that 20% of the sample in plastic bags had been lost after the same time period. Various materials may be useful as sampling bags, but the user should be aware of possible sample loss and evaluate the integrity of the sample in the bags.

(5) Sampling with Analytical Devices

Air samples may be drawn directly into analytical devices such as infrared (IR) analyzers, indicator solutions, indicator tubes, and combustible gas analyzers. These methods will be discussed in the following section and may be useful when immediate results are needed, automatic continuous monitoring is desired, or precision and accuracy are not critical.

(b) Analytical Methods

(1) Spectrophotometric Methods

Measurement of the absorption of light by styrene is the basis of spectrophotometric methods [98,236,237,239]. Spectrophotometric determinations are subject to interference from compounds of similar structure but can be used when the other components present are known or can be shown not to interfere. In cases where other compounds are present, it is necessary to determine their interference with the styrene absorption spectrum. For example, if styrene were to be analyzed by IR spectrophotometry in the presence of butadiene, a wavelength of 11 μm would not be appropriate since butadiene also absorbs light at this wavelength.

(2) Colorimetric Methods

Although styrene does not absorb visible light, the formation of a colored derivative has been used to permit colorimetric analysis [98,238,242,243,244,246,248]. The usual requirements of such a method (i.e., the color-producing reaction must be quantitative and specific for the compound being analyzed, the color must be stable long enough to permit measurement of color intensity, and the color intensity must be

proportional to the concentration of the material being analyzed) have not been difficult to meet with styrene except that color stability has often been poor, necessitating prompt analysis [242].

(3) Polarographic Methods

Polarography [99] is an electroanalytical method in which the analyte undergoes an oxidation or a reduction reaction at an electrode. The potential at which the reaction occurs is a function of the structure of the analyte and the current produced is generally proportional to its concentration. Styrene cannot be determined in aqueous solution by this method because water is reduced before styrene. However, a derivative formed by the reaction of styrene with nitrous acid has been shown to be reducible in an aqueous medium [99]. The interferences from other unsaturated compounds and the completeness of the derivatization have not been extensively studied.

(4) Chromatographic Methods

Chromatography [35,241,247,249,250,251,254,255,256,260,266,267], including gas, thin layer, and paper methods, can separate a mixture into its component parts in addition to measuring the amounts of each. Gas chromatography is the best of these methods because results are easier to quantify than with the others. Interferences can usually be circumvented by changing the carrier gas flow rate, column temperature, or column packing material. Unequivocal identification of each component can be made by a combination of gas chromatography and mass spectrometry [250]. Portable gas chromatographs are available. Detailed analytical methods for styrene have been developed [249,254,256,259].

(c) Methods that Combine Sampling and Analysis

Instruments that combine sampling and analysis in one operation include combustible gas indicators [35], IR analyzers [69], and direct-reading colorimetric devices [35,243,244,261]. An advantage of these methods is that concentrations are immediately known. The methods are useful for determinations of styrene concentrations before workers enter confined spaces, for detection of leaks, etc.

Combustible gas indicators measure total combustible gases in the air, and may be used to determine styrene where it is known to be the only or the predominant combustible vapor present in the air. IR detectors [69] are capable of some selectivity because they can monitor a selected IR wavelength to measure concentrations of the desired compound in the presence of others that do not absorb in that region. Styrene has its strongest absorbance in the region of 10-15 μm, as, for instance, do butadiene, acrylonitrile, and methyl methacrylate. An analytical wavelength at which interference is minimal must be selected. Direct-reading colorimetric tubes [35,121,261] and colorimetric indicator solutions [243,244,261] have also been used for styrene determination.

(d) Recommendations

It is recommended that the method developed by NIOSH [259] for styrene collection on charcoal with analysis by gas chromatography be used to measure worker exposure to styrene. Under certain circumstances, the use of other methods such as direct-reading colorimetric devices [35,243,244,261] to obtain an indication of styrene concentration before entering a confined space may be useful. Similarly, a combustible gas indicator [35] can be useful, especially where specificity and accuracy are less important and where concentrations based on brief sampling are needed (e.g., peak or ceiling concentrations).

Charcoal is recommended as the adsorbent for collection of styrene because it has been tested and found to collect styrene efficiently, because tubes containing suitable charcoal are commercially available, and because removal of styrene from charcoal can be nearly quantitative. Gas chromatography is recommended as the analytical method for styrene because it is reliable and very sensitive. Although testing has not been extensive at low concentrations, the data indicate that the analytical lower limit may be less than 100 µg per sample [252,259]. This corresponds to approximately 2.5 ppm in a 10-liter air sample. If greater sensitivity is required, substitution of thermal for liquid desorption could be used [249]. Field studies with both silica gel [107] and charcoal (FA Madsen, written communication, December 1976) and laboratory studies with charcoal [254,258] indicate that styrene is stable on solid sorbents.

Styrene can be collected efficiently on charcoal at rates of 1 liter/min or less. Sampling at 1 liter/min for 15 minutes should provide an adequate sample for measuring ceiling concentrations. At a styrene concentration of 25 ppm, sampling at 1 liter/min for more than 4 hours might result in sample loss; sampling at about 250 ml/min is recommended for measuring TWA exposures if long sampling times are used. Appendix I gives specific directions on the recommended methods of sampling and analysis.

In operations where styrene and peroxides may be mixed, sampling for styrene oxide should be conducted as part of a program to investigate the possible role of styrene oxide in the production of mutations, terata, abortions, and cancer. Styrene oxide can be sampled and analyzed by a recently developed NIOSH analytical method [268]; other methods have also been used successfully [233,269].

Biological Monitoring of Exposure

There are circumstances where biological evaluation of worker exposure to styrene is a desirable adjunct to environmental monitoring. Increased styrene absorption may occur with increased respiration [88]. An instance of possible styrene exposure during its use in a nonoccupational situation (i.e., repair work with reinforced plastics at home) has been described in the Case Studies and Miscellaneous Reports Section [66], and there is also

a possibility of ingesting styrene present in foods and beverages because of careless work practices. Biological monitoring in conjunction with environmental monitoring can aid in identifying and eliminating other such sources of styrene absorption. Biological evaluation of exposure may also be a valuable adjunct to environmental monitoring in situations such as RP/C processes where skin contact with styrene-containing resins is common and inhalation exposures to styrene are especially variable.

Several experimental studies and one occupational study, which have been described in Chapter IV, discussed the elimination of styrene in the breath of individuals after exposure [35,69,71,72,88,146]. Only 2-3% of the amount of styrene absorbed is eliminated in the breath as unchanged styrene during several days after removal from exposure. While breath analysis can unequivocally establish that exposure to styrene has occurred [69,70], concentrations in alveolar air have not been well correlated with arterial concentrations. In 1974, Astrand et al. [88] found a poor relationship between alveolar and arterial styrene, but because they believed arterial and capillary styrene concentrations were in good agreement they recommended fingertip blood samples be taken and analyzed for styrene. For biological monitoring, Hake et al. [70] preferred analysis of alveolar air for styrene, with sampling being performed 15 minutes after exposure and analysis performed the same day. Stewart et al. [69] noted a rapid decrease in alveolar styrene concentration such that 4 hours after exposure at 117 ppm only about 0.1 ppm styrene was found in exhaled air. Because of this and the marked slope of the decay curves [35,69,88], breath analysis does not adequately estimate exposures unless conditions, especially time of sampling, are well controlled.

As described in Chapter IV, urinary mandelic acid has been demonstrated to be the major metabolite of styrene in humans [143,144]; the amount excreted in the urine reflects the amount of styrene absorbed from respiration [88,143,144,156] and, to a lesser degree, contact with the skin [151,152,153]. Mandelic acid excretion in the urine has been studied extensively in subjects not exposed [35,79,121,159] and in workers and others exposed to styrene [35,75,79,90,92,109,121,125,156,159,270,271,272, 273]. Phenylglyoxylic acid, which is a metabolite of mandelic acid, has also been found in the urine of workers and experimental subjects exposed to styrene [35,83,90,121,144,156,159,270,271].

Other investigators [68,121,159] have evaluated urinary hippuric acid concentrations after styrene exposure. However, in one study [159] hippuric acid was found to be a poor indicator of styrene exposure unless the styrene concentration was greater than 100 ppm, and, in another study [121], no increase in hippuric acid concentration was found after exposure to styrene at 30 ppm.

Methods that have been developed to measure urinary mandelic and phenylglyoxylic acids include polarography [144], colorimetry [121,270], paper chromatography [122,144], gas chromatography [79,89,122,158,274,275, 276,277], fluorometry [278] and isotachophoresis [279].

In a method described in 1964 by Bardodej [144], mandelic acid was converted to benzaldehyde, which was steam-distilled and analyzed by polarography. Other substances that can be converted to benzaldehyde and thus interfere with this analysis method include phenylglycol and its glucuronide, styrene oxide, aminophenyl acetic acid, phenylalanine, and phenylpyrotartaric acid. In urine samples from unexposed subjects, measurements equivalent to 20 mg mandelic acid/liter were found by Bardodej [144]. In 1967, Huzl et al. [109] used the method of Bardodej [144] and found a relationship between mandelic acid in urine collected during the second half of the workshift and concentrations of styrene measured on single occasions in various workplaces. In 1974, Burkiewicz et al. [272] studied mandelic acid excretion and styrene exposures in workers for 1 week also using the method of Bardodej [144]; no mandelic acid was found in urine samples from 30 unexposed workers. About 436-1,630 mg mandelic acid/liter of urine was found in samples collected during the last 3 hours of work from workers with average styrene exposures of 28-110 ppm. In 1970, Sedivec and Flek [274] used the method of Bardodej [144] to convert mandelic acid to benzaldehyde, but assayed benzaldehyde by gas chromatography rather than by polarography.

Bardodej [144] also described a colorimetric method for analysis of mandelic acid that was based on the reaction of mandelic acid with ferric chloride. Endogenous substances that may interfere with this analysis method are lactic acid, pyrotartaric acid, acetoacetic acid, beta-hydroxybutyric acid, atrolactic acid, and phenylpyrotartaric acid. Thiocyanates, some indole derivatives, and salicylic acid may also interfere. Using the colorimetric method, there were only trace amounts of mandelic acid in urine from healthy unexposed people. This method [144] was studied using workers from various industries who were exposed to styrene at average concentrations of about 20-80 ppm. At the lowest exposure, urinary mandelic acid concentrations were about 200 mg/l and, at the highest exposure concentrations, about 1,600 mg/l.

In 1970, Ohtsuji and Ikeda [121] reported the quantitative reaction of mandelic and phenylglyoxylic acids with a sulfuric acid-formalin reagent. Mandelic acid was measured colorimetrically at 450 nm and phenylglyoxylic acid at 350 nm. When Horiguchi and Teramoto [271] studied this method in 1972, they found that normally occurring substances in urine such as cholesterol, and hydroxyphenylacetic, phenylacetic, vanillic, and ferulic acids would also react with the sulfuric acid-formalin reagent. Because of such interferences, urine samples from unexposed people have indicated concentrations of mandelic acid of 22-698 mg/l [35,79,88,121,159,270,271]. In 1972, the method of Ohtsuji and Ikeda [121] was also used to evaluate industrial exposures by Gotell et al. [35], who found better correlation between 8-hour TWA exposures and urinary mandelic acid concentrations than between the TWA exposures and urinary phenylglyoxylic acid concentrations. However, the data were not linear over the range of the TWA exposure concentrations (17-292 ppm). In 1974, Harkonen et al. [270] also found that urinary mandelic acid concentrations correlated better than phenylglyoxylic acid with TWA exposures to styrene at concentration up to 150 ppm; the data

were also not linear over the range of TWA exposures. Harkonen et al. [270] concluded that because of the variation in the results, the probability of a worker being exposed at less than 50 ppm could not be calculated with precision when using this colorimetric method.

In 1973, Slob [280] used paper chromatography to separate mandelic acid and used gas chromatography of the silyl derivative to measure it. With these techniques, 0.5-10 mg of mandelic acid were found to have been excreted in urine during 8 hours by workers exposed to styrene at about 1 ppm.

In 1974, Buchet et al. [89] and Vivoli and Vecchi [275] described gas chromatographic methods that involved methylation of mandelic and phenylglyoxylic acids. With these methods neither mandelic acid nor phenylglyoxylic acid were found in the urine of unexposed subjects. In styrene-exposed workers the concentrations of both acids using these methods were related to exposure [90,275].

In 1976, Bauer and Guillemin [277] used gas chromatography after methylation of the acids with diazomethane as described by Buchet et al. [89]. They discovered, however, that unless the conditions for methylation were precisely controlled, conversion of phenylglyoxylic acid to its methyl ester was not quantitative (a possible explanation for the relatively poor recoveries of phenylglyoxylic acid found by Saeki [276] in another study).

In 1980, Flek and Sedivec [281] described a method for the simultaneous determination of mandelic and phenylglyoxylic acids in urine. Urine was saturated with ammonium sulfate and acidified, and the two acids were then extracted with ethyl acetate. The mandelic and phenylglyoxylic acids were converted into methyl esters with diazomethane, and then analyzed by gas chromatography. The investigators [281] found no interferences from other urine components. The methyl ester of hippuric acid was found to have a much longer retention time under the specified chromatographic conditions, and thus did not interfere. The lower limits of detection of the two acids were about 10 µg/ml. Flek and Sedivec [281] believed the use of an iodine indicator to show completion of esterification, with the supply of diazomethane then being shut off, corrected the potential of methylation problem described earlier by Bauer and Guillemin [277].

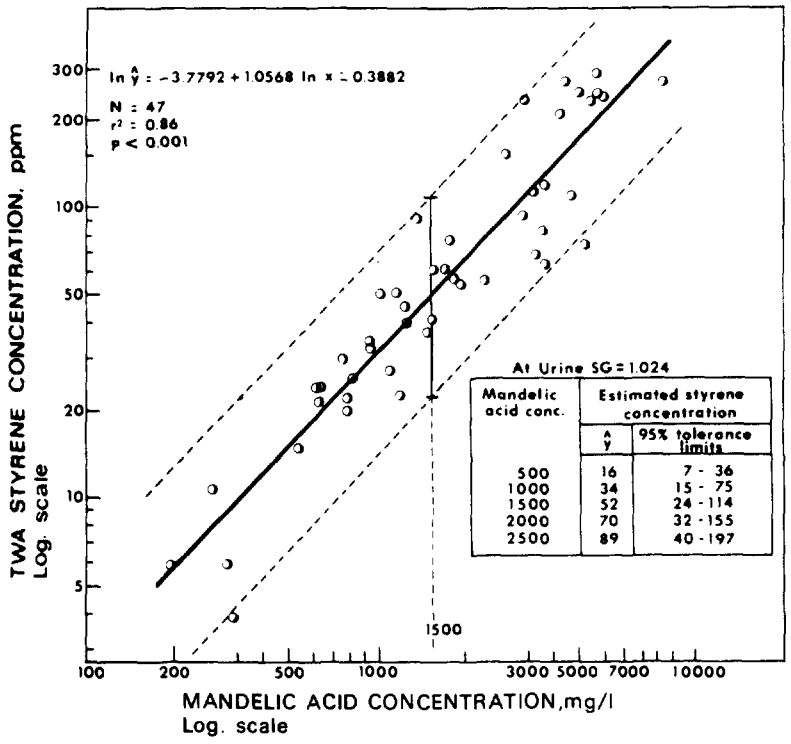
In 1974, a procedure for analysis of the silyl derivative of mandelic acid by gas chromatography was described by Engstrom and Rantanen [79]. They found 94% recovery of mandelic acid that had been added to urine; the coefficient of variation of 10 replicate analyses of the urine of a worker who made plastics was 2%, and the lower limit of detection was 1 mg/l. However, mandelic acid was found in the urine of 10 people who had no history of styrene exposure. The method of Engstrom and Rantanen [79] has been studied extensively in styrene-exposed workers [75,79,92,125], and in control subjects [79,92]. The sensitivity of the method is less than that of the method of Slob [280], but there is a good relationship between

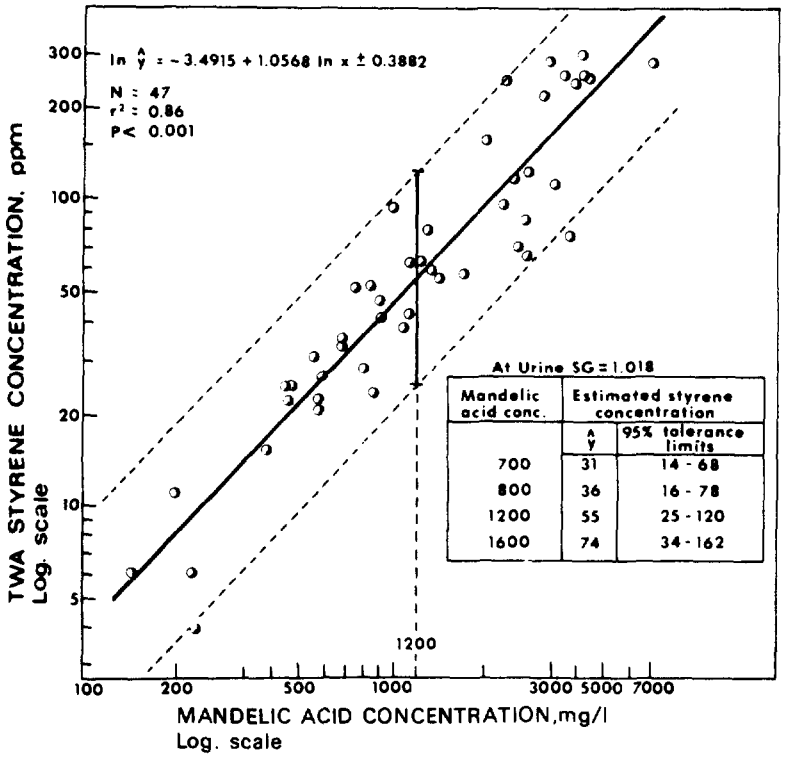
average TWA styrene exposures and urinary mandelic acid concentrations in workers exposed to styrene in the range of about 5-300 ppm [79,92,125], as shown in Figure V-1 on p. 141. The lower figure, representing the regression of mandelic acid with styrene at a urine specific gravity of 1.018, has been copied with permission from the report of Harkonen et al. [125]; the upper figure represents the same regression at a urine specific gravity of 1.024.

In 1976, Saeki [276] also described a method for analyzing the silylated derivatives of mandelic and phenylglyoxylic acids by gas chromatography. By this method, recoveries were 95-100% for mandelic acid and 73-91% for phenylglyoxylic acid. Apparently the method was not used to evaluate exposures of workers.

In 1979, Chakrabarti [278] described a method of analysis of mandelic and phenylglyoxylic acids in urine by fluorometry, after extraction into ether and separation of the acids by thin-layer chromatography. The fluorescent derivatives formed by treatment with concentrated sulfuric acid were described as highly stable. The limits of detection of both acids were 2 μg/ml of urine, with coefficients of variation being less than 15%.

Figure V-1 TWA STYRENE CONCENTRATION VERSUS URINARY MANDELIC ACID CONCENTRATION
(Taken from Harkonen et al [125])





An isotachophoretic method for analysis of urine samples for mandelic, phenylglyoxylic, hippuric, and methylhippuric acids was described in 1977 by Sollenberg and Baldesten [279]. The analytical range was 0.5-35 nmol/0.5 ml sample for each acid. With this method, mandelic acid was not found in the urine of 14 control subjects, but phenylglyoxylic acid at concentrations of 144 and 196 nmol/ml was found in the urine of two subjects. Good agreement was found when some samples were also analyzed by gas chromatography [279].

In a 1979 study of biological monitoring, Fields and Horstman [282] evaluated the styrene exposures of two groups of workers by (1) the sampling and analysis of workers' breathing zones, (2) the sampling and analysis of expired breath at the end of the workshift, and (3) the analysis of urine samples collected just before and just after the workshift, as well as at various times after the shift was over. Both study groups made fibrous glass reinforced boats. The first group consisted of five healthy males, 19-23 years of age, who had been employed making reinforced plastic boats for 2 weeks to 18 months. The second group consisted of 18 healthy males, aged 19-48 years; the authors did not state how long this group had worked. These men in the second group occasionally wore double cartridge organic vapor respirators during some phases of their work.

The investigators [282] found a poor correlation ($r=0.234$) between airborne styrene concentrations and alveolar air concentrations. Urinary mandelic acid was analyzed by the gas chromatographic method of Engstrom and Rantanen [79]; data were categorized by whether or not respirators were worn, and were calculated in terms of three specific gravities, i.e., the two most commonly used literature values of 1.024 and 1.018, and the mean specific gravity of the 62 postshift urine samples, 1.033. For the group not wearing respirators, a correlation coefficient of 0.85 between urinary mandelic acid and airborne styrene exposure was found. With those wearing respirators, there was a poorer correlation ($r=0.57$). These coefficients were the same regardless of which specific gravity adjustment was used. For the group not wearing respirators, a urinary mandelic acid concentration of 1,655 mg/l (adjusted to a specific gravity of 1.024) was equivalent to a styrene exposure of 100 ppm, with 95% confidence limits of 83-117 ppm styrene. Stated another way, an 8-hour TWA exposure of 100 ppm was equivalent to a urine mandelic acid concentration of 1,275-2,063 mg/l. Fields and Horstman [282] also estimated from daily urinary excretion data that mandelic acid concentrations increased slightly through the week, indicating that the amount of mandelic acid excreted in urine sampled at the end of the shift depends largely on that day's absorption and partly on absorption on previous days. In this study [282], there was a markedly better correlation between urinary mandelic acid excretion and styrene exposure than between expired styrene and styrene exposure; thus, mandelic acid excretion would be expected to be a superior method of biological monitoring.

The study of Hake et al. [70] on biological monitoring was reviewed in Chapter IV. These investigators [70] concluded that blood analysis for

styrene, analysis of urinary metabolites, and alveolar breath analysis for styrene were all useful indices of exposure to styrene, though the investigators preferred analysis of alveolar air samples taken 15 minutes after exposure. Hake et al. [70] exposed volunteers at known and, except for one experiment, relatively constant concentrations, whereas the workers studied by Fields and Horstman [282] were performing regular work and exposed at variable concentrations.

As part of the investigation of the workers in a reinforced plastics workshop, Brooks et al. [91] in 1979 and Elia et al. [283] in 1980 described biological monitoring. Post-shift urine samples were collected within 30 minutes of the end of the shift, and analyzed for mandelic acid by the gas chromatographic method of Guillemin and Bauer [158]. Phenylglyoxylic acid was analyzed by reduction with zinc followed by measurement as mandelic acid. Both groups of investigators [91,283] studied correlations of urinary metabolites with airborne styrene in terms of types of coordinates (log-log or linear plots), in terms of mandelic acid alone or the sum of the concentrations of mandelic and phenylglyoxylic acids, and in terms of adjustment for urine dilution either by adjusting for urine specific gravity or by analyzing urine creatinine and expressing results as mass of metabolites per gram of creatinine.

A linear plot of the sum of urinary mandelic and phenylglyoxylic acids vs. airborne styrene concentrations gave a correlation coefficient of only 0.74. All other comparisons gave higher correlation coefficients and involved log-log plots. Log of the sum of the two acids vs. log of the airborne styrene gave r=0.96 when urine dilution was corrected for creatinine, 0.95 when urine dilution was corrected by adjusting urine specific gravity to 1.024, and 0.93 when urine dilution was not corrected. Log of the concentration of mandelic acid only vs. log of the airborne styrene gave r=0.96 when urine dilution was corrected for creatinine, r=0.95 when urine was adjusted to a specific gravity of 1.024, and r=0.94 when urine dilution was not corrected.

These investigators [91,283] concluded that the most effective monitoring of workers exposed to styrene included both biological monitoring and monitoring of airborne exposures; they believed monitoring of post-shift urine samples for metabolites should involve analysis for both acids and that adjustments for urine dilution by correction for either creatinine content or specific gravity should be made.

In 1974, Engstrom and Rantanen [79] compared the results of their gas chromatographic method with the results of the colorimetric method of Ohtsuji and Ikeda [121]. With parallel analyses of urine samples from 10 subjects not exposed to styrene, no mandelic acid was found by gas chromatography whereas 46-698 mg/l were found by the colorimetric method. With parallel analyses of urine samples from 35 plastics workers, the results from the two methods had a correlation coefficient of 0.98 and an average difference of 254 mg/l. It appears that despite the lack of specificity offered by colorimetric methods [121,144], they may be

useful. Application of a colorimetric method may be of particular importance in those situations where appreciable skin contact is possible and where other equipment such as a gas chromatograph is not readily available. With the method of Ohtsuji and Ikeda [121], Harkonen et al. [270] found that the average urinary mandelic acid concentration at a specific gravity of 1.018 associated with an 8-hour TWA exposure of 50 ppm was about 1,660 mg/l. However, the lower 97.5% confidence limit of the mandelic acid concentration for an individual exposed at 50 ppm was below the background of the method, so that the probability of an individual being exposed at less than 50 ppm cannot be calculated with precision from colorimetrically determined mandelic acid concentrations. It is possible that the colorimetric method of Bardodej [144] is at least as accurate and precise as the method of Ohtsuji and Ikeda [121]; however, it has not been as thoroughly evaluated.

When a gas chromatographic method such as that of Engstrom and Rantanen [79] is used to determine mandelic acid concentrations, 500 mg of mandelic acid/liter of urine (corrected to a specific gravity of 1.018) may indicate a recent exposure to at least 10 ppm styrene. From Figure V-1 (see p. 141) a concentration of 1,200 mg mandelic acid/liter of urine (adjusted to a specific gravity of 1.018) corresponds to an average 8-hour TWA styrene exposure estimate of 55 ppm, with 95% confidence limits of about 25-120 ppm. Thus, mandelic acid concentrations in excess of 1,200 mg/l, as determined by the method on Engstrom and Rantanen [79], indicate with 97.5% statistical confidence that styrene absorption was in excess of that from an 8-hour TWA exposure to styrene at 25 ppm. The average mandelic acid concentration (i.e., the point estimate) corresponding to an 8-hour TWA concentration of 50 ppm is about 1,100 mg/l.

Of the various urinary excretion products of styrene, mandelic acid and phenylglyoxylic acid are the most useful for biological monitoring. Although both acids can be analyzed, analysis of just mandelic acid can give useful results [156]. Because the decay curves of urinary metabolites are not as steep as the decay curves of styrene elimination in exhaled air, the time of sampling is less critical. Furthermore, variations in exposure concentrations during the workday should cause fewer variations in urine metabolite elimination than in styrene excretion in exhaled air. The urinary metabolite concentration is more likely to reflect total absorbed dose than is alveolar styrene when workday exposure concentrations have fluctuated.

When evaluating styrene exposure from mandelic acid data, consideration should also be given to pulmonary ventilation, other sources of mandelic acid such as environmental exposure to ethylbenzene [216] or phenylethanol [156], and the metabolism of alpha-hydroxybenzylpenicillin [284]. The suggested analytical method for mandelic acid in urine is described in Appendix II.

Medical Surveillance

Styrene has been shown to have effects on the central nervous system (CNS) and on the skin, eyes, and upper respiratory tract; furthermore, although the evidence is not strong styrene exposure may affect liver function. Thus, preplacement and periodic medical surveillance should include physical examinations and medical and work histories directed to ascertaining the status of the CNS, skin, upper respiratory tract, and the liver. Specific tests, except for serum enzyme assays for assessment of liver status, are not proposed, because other tests are not sufficiently specific or available.

Although the data on teratogenicity and on spontaneous abortions, discussed in Chapter IV, have not been confirmed, they are sufficiently suggestive to warrant, as a prudent preventive measure, advising workers of this information and on the possible risks that could be associated with exposure to styrene during pregnancy.

Biological monitoring of styrene exposure by the analysis of urine for mandelic acid may be a useful adjunct to the environmental monitoring of exposures, especially where breathing zone monitoring does not adequately represent a worker's exposure, for example, where great excursions in airborne concentrations are not detected or where significant percutaneous absorption may occur. Because of the likelihood of both of these occurring in reinforced plastics fabrication (RP/C) operations, biological monitoring may be especially useful there. It may be best to establish the acceptable limit of mandelic acid excretion, in relation to the permissible exposure limit, in each plant, with consideration to the analytical method and, perhaps, sampling circumstances. Pending such a determination, Figure V-1 (see p. 141) can be used for guidance in setting limits of acceptable mandelic acid excretion. Where this biological monitoring indicates excessive styrene absorption, an investigation of the source of the excessive exposure should be initiated. If the cause resulted from failures of engineering controls (leading to excessive exposures) or work practices (leading to ingestion or skin exposure), appropriate corrective action should be taken. If personal habits are the cause (for example, from home activities such as hobbies that lead to additional exposure), the worker should be counseled.

Styrene Oxide in Some Styrene Operations

Two 1979 reports [233,269] described finding styrene oxide at low concentrations in the workroom air in factories making reinforced plastic objects. In the study in Finland by Pfaffli et al. [269], air samples were collected on charcoal, desorbed with dichloromethane, and assayed by capillary gas chromatography with a flame ionization detector. Styrene oxide concentrations were about the same in both personal and general air samples; concentrations were 0.04 ppm in hand lay-up and 0.12-0.17 ppm in spray operations, when styrene concentrations were 59-133 ppm. In the study

in Norway by Fjeldstad et al. [233], personal samples were collected on charcoal, desorbed with carbon disulfide, and analyzed by gas chromatography with a flame ionization detector; confirming analyses were made by high performance liquid chromatography. Styrene oxide concentrations ranged from less than 0.003 ppm to 0.086 ppm; styrene concentrations were 17-289 ppm.

The investigators [233,269] believed that the styrene oxide was formed by the mixing of styrene with peroxides added as curing agents. This seems reasonable, inasmuch as one method of synthesis of epoxides is to react olefins with peroxides.

Thus, it is important to evaluate styrene oxide exposures in work areas where peroxides and styrene are mixed, in view of the toxic problems (i.e., mutagenicity and carcinogenicity) posed by styrene oxide.

In addition to the methods of sampling and analysis for styrene oxide described in the two Scandinavian reports [233,269], a method was developed in 1979 by the Los Alamos Scientific Laboratory under NIOSH sponsorship [285]. Samples were collected in a tube holding a glass fiber filter followed by a sorbent, Tenax-GC. The styrene oxide was desorbed with ethyl acetate and analyzed by gas chromatography with a flame ionization detector. Recoveries of greater than 95% were reported at a relative humidity of 80% with samples of 0.5-44 µg. The limit of detection of the analytical method was 0.1 µg/sample.

VI. DEVELOPMENT OF OTHER OCCUPATIONAL HEALTH STANDARDS

The first recommendation for a worker exposure limit for styrene was by Spencer et al. [53] in 1942. Although they wrote that repeated exposures to styrene at 650 ppm would "probably produce no serious disturbances in man," they recommended 400 ppm as a permissible limit, which Spencer et al. [53] reported had a disagreeable odor but would not cause appreciable eye or nose irritation. In 1943, Mallette [54], in discussing industrial hygiene in synthetic rubber manufacture, pointed out that 200 ppm was a preferable upper limit of styrene exposure because of the eye and nose irritation experienced by workers at 400 ppm.

In 1944, the American Standards Association (ASA) published its American War Standard Allowable Concentration of Styrene Monomer [286]. The recommended maximum allowable limit was 400 ppm for exposures not exceeding a total of 8 hours daily. The report by Spencer et al. [53] was cited, but it was noted that the limit was based on animal experiments and that there had not been sufficient experience with humans to evaluate the response of man.

In 1945, Cook [287] compiled a list of maximum allowable concentrations (MACs) of atmospheric contaminants of several American governmental agencies. Five of the State agencies recommended a MAC of 400 ppm of styrene, but Cook [287] recommended that the value be lowered to 200 ppm because workers had experienced irritation at 400 ppm.

In 1946, the American Conference of Governmental Industrial Hygienists (ACGIH) endorsed the ASA styrene standard of 400 ppm, along with 15 other ASA standards, because they considered that that values had been established and substantiated by the necessary scientific research [288]. In 1947, the ACGIH proposed lowering the MAC to 200 ppm [289]; reasons for the recommendation were not given. In 1956, the ACGIH reported that recommendations for changes in the values of a number of substances had been made [290], among them a change in the value for styrene from 200 to 100 ppm. Subsequent to the 1947 recommendation [289], the terminology for an environmental limit had changed from MAC to Threshold Limit Value (TLV) defined as "the maximum average atmospheric concentration to which workers may be exposed for an eight-hour working day without injury to health" [290].

In 1957, the ACGIH adopted a TLV of 100 ppm [291]. The notation "skin" was added in 1961 by the ACGIH to the TLV of those substances which in liquid form could penetrate the skin and cause systemic effects; styrene was not so noted [292]. In 1962, reports by Spencer et al. [53], Carpenter et al. [68], and an industry bulletin were cited by the ACGIH in support of the styrene TLV of 100 ppm. In 1964, the ACGIH changed the TLV of 100 ppm for styrene from a TWA value to a ceiling value that should not be exceeded [293]; the basis for the change was not given.

In 1967, the ACGIH proposed lowering the TLV for styrene to 50 ppm [294], and it was so listed under "Notice of Intended Changes" in the 1967 and 1968 TLV lists [295,296]. However, the ACGIH decided in 1969 that the TLV for styrene should remain at 100 ppm but as a TWA, i.e., with the removal of the ceiling notation [297]. According to the 1969 ACGIH transactions [298], the recommendation of 100 ppm was based on the experimental human exposure studies of Stewart et al. [69]. The ACGIH [298] stated that, in the study cited [69], none of the subjects exposed at 50 ppm for 1 hour had experienced any symptoms or had abnormal clinical findings; however, exposure at 100 ppm produced mild untoward, but transient, subjective responses in half the subjects exposed. In 1981, the ACGIH [299] decided to change the styrene TLV to 50 ppm with a short-term exposure limit (STEL) of 100 ppm. A TLV of 50 ppm, noted by the ACGIH in their 1980 Documentation of the TLVs [300] as being one-tenth the lowest concentration possibly causing lymphoid or hematopoietic tumors in female rats studied by Jersey et al. [195], and a STEL of 100 ppm were suggested as being reasonable.

Documentation of MAC in Czechoslovakia [301] was published in 1969. The suggested styrene limit was 47 ppm for an average exposure, which was considered to be adequate to prevent chronic poisoning, and 235 ppm for a peak exposure, which was considered adequate to prevent narcotic symptoms. In support of the recommendations, 12 references were cited, including those by Bardodej et al. [97,143], Carpenter et al. [68], and Spencer et al. [53].

In 1970, the American National Standards Institute, Inc., (ANSI) published a standard, Z37.15-1969, for acceptable concentrations of styrene [302]. There were three components, all assuming an 8-hour workday: (1) an acceptable TWA for protection of health; (2) an acceptable ceiling concentration for protection of health; and (3) acceptable maximum peaks above the acceptable ceiling. The ANSI values were a TWA concentration of 100 ppm, a ceiling of 200 ppm (provided the TWA was not exceeded), and maximum peaks of 600 ppm for a duration of not more than 5 minutes once every 3 hours. These recommendations were based on the reports of Spencer et al. [53], Carpenter et al. [68], Wolf et al. [162], and Stewart et al. [69].

The 1969 ANSI Z-37 limit [302] was adopted in 1971 as the Federal OSHA standard (29 CFR 1910.1000, Table Z-2). It consists of a TWA concentration of 100 ppm for an 8-hour day, a ceiling concentration of 200 ppm, and a maximum peak of 600 ppm for no more than 5 minutes in any 3 hours.

A Scandinavian expert group consisting of representatives from Denmark, Finland, Norway, and Sweden, published a review [303] of much of the scientific and technical literature on styrene which included the hygienic limit values in force in various countries. According to their tabulation, 100 ppm was the limit in Australia, Belgium, Finland, Yugoslavia, the Netherlands, Switzerland, Great Britain, and the United States (OSHA); 72 ppm in Italy; 50 ppm in Denmark, Norway, and Japan; 47 ppm in Romania,

Czechoslovakia, and the German Democratic Republic; 24 ppm in Poland; 12 ppm in Hungary; and 1 ppm in Bulgaria and Russia [303]. The MAK value (maximum concentration value in the workplace) for styrene in the Federal Republic of Germany is 100 ppm [304]. In 1981, Sweden [305] adopted a TWA styrene standard of 25 ppm with a 15-minute short-term value of 75 ppm; styrene was designated as being easily absorbed into the body.

VII. ASSESSMENT OF EFFECTS

The principal health effects due to styrene exposure involve the central nervous system. These effects include subjective complaints of headache, fatigue, dizziness, confusion, drowsiness, malaise, difficulty in concentrating, and a feeling of intoxication. Objective signs of these effects are altered equilibrium, delayed reaction times, and abnormal EEGs. Local irritation of the eyes, nose, and respiratory tract and skin irritation are also widely acknowledged as effects of styrene exposure. There have also been reports of liver injury, peripheral nervous system dysfunction, abnormal pulmonary function, chromosomal changes, reproductive effects, and carcinogenicity related to styrene exposures. Although data concerning these latter adverse effects are not well defined at this time, they do provide cause for concern.

Experimental studies have provided some of the evidence of adverse health effects related to styrene. Two human subjects experimentally exposed to styrene at 800 ppm for 4 hours experienced eye and throat irritation immediately [68]. Listlessness, drowsiness, and impaired balance occurred during exposure, and subjects were weak, unsteady, and responded poorly after the exposure [68]. During a one-hour exposure at 376 ppm, five human subjects experienced eye or respiratory tract irritation within 20 minutes, and decrements in tests of balance, coordination, and manual dexterity were measured [69]. Subjective complaints of headache, nausea, and a feeling of slight inebriation were also reported during the same study [69]. At 216 ppm, one of three subjects noted nasal irritation after 20 minutes of exposure [69]. In another experiment [71], simple psychomotor reaction times increased for the twelve subjects, but only after consecutive 30-minute exposures at 50, 150, 250, and 350 ppm styrene (i.e., an average of 200 ppm during the two-hour testing period). Eye irritation, slower reaction times, and loss of balance were found in subjects during a 90-minute exposure at 200 ppm [72].

Some of these experimental studies of human subjects have also demonstrated adverse effects of styrene exposure at concentrations as low as 100 ppm. Slower reaction times (26-28%) were found in three subjects during a 90-minute exposure at 100 ppm [72]. In the same study [72], six subjects who received a total of 13 exposures of 90-minute duration at 100 ppm styrene noted sleepiness (92% of the exposures), fatigue (77%), headache (77%), difficulty concentrating (69%), malaise (54%), nasal irritation (54%), and nausea (38%). In an experimental study that lasted 6 weeks, the investigators [70] stated that there were changes consistent with CNS depression; three of the six subjects had both visual evoked response and EEG amplitude changes after exposures at 20, 100, and 125 ppm styrene. In the same study [70], the incidence of eye, nose, and throat irritation for the ten male subjects was 13% at 0 ppm, 17% at 20 ppm, 20% at 100 ppm, 33% during exposures fluctuating between 75 and 125 ppm, and 45% at 125 ppm styrene. The incidence of eye, nose, and throat irritation for the two female subjects was 8% at 0 ppm and 32% at 100 ppm [70]. In another study [69], three of six subjects noted mild eye or throat irritation during the

first 20 minutes of a 7-hour exposure to 99 ppm styrene; the irritation subsided after an additional 30 minutes. In addition, both simple visual and audiovisual choice reaction times in tests of two subjects were 22-25% slower during a 90-minute exposure at 50 ppm styrene [72]. During a total of 6 exposures each of 90-minute duration at 50 ppm in the same study, the subjects noted eye irritation, fatigue, and difficulty concentrating during 67% of the exposures, and headache during 50% of the exposures; the incidence of these complaints during exposures at 0 ppm was 10-20%.

The experimental study by Oltramare et al. [72] provides some evidence of CNS depression, manifested by subjective complaints and delayed reaction ability in human subjects exposed to styrene at 50 ppm and 100 ppm. The experimental studies by Oltramare et al. [72], Hake et al. [70], and Stewart et al. [69] indicate that styrene irritates the eyes, nose, and throat of some subjects at 100 ppm and a few subjects at concentrations as low as 50 ppm.

There are many clinical studies demonstrating these same CNS and irritation effects, as well as other health effects, among styrene-exposed workers. Subjective complaints indicative of CNS depression have been noted in numerous studies [94,101,105,106,109,110,112,113,123,138]. Although no exposure data were given, 68 of 70 workers in a Russian RP/C plant [101] complained of constant headache increasing throughout the day with fatigue and sleepiness increasing after the workshift, while 46 of the 70 workers complained of nausea, dizziness, and heart pain. In a study of 128 Czechoslovakian RP/C workers exposed to styrene at TWA concentrations of 4-195 ppm [105], 20% reported headache, 15% reported tiredness, and 13% reported symptoms of drowsiness. Similarly, higher incidences of unusual tiredness, reduced short-term memory, giddiness, and headache were reported among 33 workers from three Swedish RP/C factories with TWA styrene exposures of 5-174 ppm, than among controls with no solvent exposures [123]. Subjective complaints were also noted among 35 Czechoslovakian RP/C workers exposed at 19-130 ppm styrene [106]; these complaints included headache (51% of the workers), fatigue (41%), and drowsiness (34%). In a U.S. RP/C factory with TWA styrene exposures of 9-111 ppm, 50% of the 22 workers complained of headache and 36% of fatigue [113]. Among 22 workers in two RP/C factories in the Netherlands who were exposed at about 24-94 ppm styrene [110], 50-90% complained of drowsiness, and 30-70% noted headache and dizziness. Headache was reported by 36% and drowsiness by 24% of 55 Czechoslovakian RP/C workers exposed at 6-94 ppm styrene [109].

Among 81 Swedish RP/C workers with TWA styrene exposures of 3-312 ppm, but with 74% less than 100 ppm [112], the following subjective complaints were reported: fatigue (60% of the workers), dizziness (38%), headache (25%), poor memory (21%), and nausea (14%). Among 27 English RP/C workers exposed to styrene at about 92 ppm, 52% felt unduly tired compared to 19% of a control group comprised of workers in the same factory, but without

exposure to styrene [138]. Complaints of frequent headaches were reported by 38% of the 40 workers in a Russian polystyrene production facility where styrene exposures sometimes exceeded 12 ppm [94].

Slower reaction times [111,392] and abnormal EEGs [118,124,125] have also been reported in clinical studies. The reaction times of seven Swedish RP/C workers with TWA exposures of 3-14 ppm styrene [392] were significantly slower ($p<0.05$) than the comparison group; however, the investigators were unable to determine whether styrene was responsible. Significantly longer reaction times as compared to age-matched controls were also found in 106 workers from four Swedish RP/C plants where TWA styrene exposures were 10-120 ppm [111].

At a Finnish RP/C facility where the average styrene exposure was estimated from urinary mandelic acid measurements to be about 30 ppm, 23 of 96 workers (24%) had EEGs judged to be abnormal [124,125]. Among 35 Czechoslovakian RP/C workers with TWA styrene exposures of 19-130 ppm, only five of eighteen EEGs given were judged to be normal [106]. In a subsequent Czechoslovakian clinical study of 21 RP/C workers [108], some had abnormal EEGs after three years of styrene exposure (concentration was not specified), whereas no abnormal EEGs were found during a pre-exposure examination. In a study of Polish RP/C workers [118], abnormal EEGs were found in 31 of 43 workers (72%) with about one year of styrene exposure at 25-75 ppm, and in four of twenty-one workers (19%) with ten years of exposure at about 75 ppm.

Styrene has also been shown to cause irritation of the eyes [35,53,58,61,104,110,113,126] and respiratory tract [35,53,56,59,93,104,113, 114,115,123,126] of exposed workers. Complaints of irritation of the eyes and nasopharynx were common in a study of 17 Swedish RP/C workers whose TWA styrene exposures were 17-292 ppm [35]. In a U.S. RP/C facility where styrene exposures were 45-550 ppm [104], complaints of eye, nose, or throat irritation were made by 34 of the 35 workers (97%) examined. Among 22 workers in two RP/C facilities in the Netherlands who were exposed at 24-94 ppm styrene, 90% complained of eye irritation [110]. Complaints of irritation of the mucous membranes of the respiratory tract were reported by 44% of the workers in a Russian polystyrene production facility where styrene exposures were characterized as sometimes exceeding 12 ppm [94]. In a U.S. RP/C facility with TWA styrene exposures of 9-111 ppm, 93% of the 14 workers interviewed complained of eye irritation, 50% of nose irritation, and 29% of throat irritation [113]. The reported incidence of throat irritation was higher in 33 workers from three Swedish RP/C factories (where TWA styrene exposures ranged from 5-175 ppm) than in controls with no solvent exposures [123]. A group of 96 Finnish RP/C workers whose average styrene exposure was estimated from urinary mandelic acid measurements to be about 30 ppm, frequently experienced irritation of the eyes and nose [126].

There is some evidence of styrene-induced peripheral neuropathy. The frequencies of distal hypoesthesia of the lower extremities and hypoactive

deep tendon reflexes increased with duration of exposure in styrene and polystyrene production workers [81]. The data presented did not clarify, however, whether the changes were due to age or to styrene exposures which, at the time of the study, were usually less than 20 ppm [81]. The findings of impaired radial nerve conduction in 15 of 80 workers and impaired peroneal nerve conduction in 12 of 73 workers was also reported [81]. Although the effects on the radial or peroneal nerve were not related to the magnitude of exposure, those effects on the peroneal nerve were related to the duration of exposure to styrene. However, these effects also could have been related to age; moreover, the changes were not statistically significant. In a Swedish study [123], 10 of 33 workers with TWA exposures of about 5-125 ppm had evidence of a mild sensory neuropathy with polyphasic response. Although the 10 affected RP/C workers were older, the investigators [123] concluded that age alone was not the cause. In a Finnish study [124], slightly abnormal nerve conduction velocities were found in 9 of 40 workers in a facility where the average styrene exposure was estimated from urinary mandelic acid to be about 31 ppm. In 4 of the 9 affected workers (1 with mononeuropathy, 3 with polyneuropathy) no cause other than styrene exposure could be found; however, there was no association between urinary mandelic acid concentration and nerve conduction velocity in the four workers with unexplained abnormalities. Neurological effects reported in a Czechoslovakian RP/C plant [106] included cranial nerve disturbances (in 91% of the workers), diminished reflexes (86%), and impaired balance (83%). Among 101 Polish RP/C workers with one year of exposure to 25-75 ppm of styrene, 26 had signs that the investigators [115] classified as autonomic nervous system disturbances; hypoesthesia, whitening of the fingers, trembling of the hands, weakened reactions, cat's eye pupils, excitability, and nystagmus were noted among the 26 workers. While the evidence for chronic nervous system damage (peripheral neuropathy or CNS changes) from styrene exposure is not strong, further study is warranted due to the importance of these effects.

The data on possible long-term respiratory effects of styrene is also limited. Among 35 U.S. RP/C workers exposed to styrene at 44-550 ppm, about half complained of wheezing, shortness of breath, or chest tightness [104]; exposure to an isocyanate (MDI), another respiratory system irritant, at 0.01-0.27 mg/cu m (the OSHA standard is a ceiling value of 0.2 mg/cu m) might have contributed to these effects. A possible relationship between styrene exposure and a history of wheezing or chest tightness was suggested in a study of workers making styrene and polystyrene [82]; there appeared to be some spirometric evidence of airway obstruction, but not significantly related to exposure. Conjunctival irritation related to styrene exposure was a complaint in 22% of these workers [82]. In a U.S. RP/C factory with TWA styrene exposures of 9-111 ppm [113], 54% of the workers complained of shortness of breath, 23% of chest tightness, and 18% of wheezing; however, ventilatory function was significantly changed during the shift only in those workers that smoked. Four cases of reduced FEV_1 were found among 21 RP/C workers exposed to styrene at approximately 75 ppm for about 10 years, but whether the cause was age, styrene exposure, or other factors was not clear [114]. In another clinical study [91], a significantly greater

number of RP/C workers had abnormal pulmonary function (i.e., FVC less than 80% of predicted values, FEV_1/FVC X 100 below 70, FEV_1 less than 80% of predicted values, and FEF(25-75) less than 70% of predicted values), when compared to unexposed workers from an electronic products plant.

Although various clinical studies [82,96,103,113,115,116,120] have suggested that styrene exposure has affected liver function, a clear relationship has not been demonstrated; clarifying research is needed. In any case, periodic screening of the liver function of styrene workers should be conducted due to the importance of this organ in the biotransformation and detoxification of toxic substances.

There is suggestive but conflicting evidence of mutagenicity by styrene. Workers exposed to styrene in reinforced plastics applications [76,129,130,131,132] had an increased incidence of chromosomal aberrations. There were more chromosomal aberrations (16.7 vs. 1.8/100 cells in controls, $p<0.001$) among 10 Finnish RP/C workers whose average styrene exposure was estimated from urinary mandelic acid measurements to be about 30 ppm [129]. In a related study of 16 RP/C workers [130], which included 8 workers from the previous study [129], a statistically significant increase in the incidence of chromosomal aberrations was found (15.1 vs. 2.0/100 cells in the controls, $p<0.001$); this was confirmed when 10 of the 16 workers were reexamined a year later and the incidence was 16.2%. In a Swedish RP/C factory with styrene exposures of 14-73 ppm [131], an increased frequency of chromosomal aberrations was also found (10.8 vs. 5.2/100 cells, $p<0.001$). In a study of an RP/C factory where styrene exposures were 8-158 ppm [132], the 39 styrene-exposed workers studied had a significantly higher incidence of chromosomal aberrations as compared with controls (7.9 vs. 3.9/100 cells, $p<0.001$). There was also a significant increase in the average frequency of sister chromatid exchanges (8.4 vs. 7.5 SCE/cell) in 20 of the same RP/C workers [132]. In another study [76], a significant excess of chromosomal aberrations in 14 RP/C workers as compared to 20 controls was also found (9.2 vs. 5.5%); styrene concentrations ranged from 50 to 300 ppm, but urinary mandelic acid concentrations for the RP/C workers were less than 1,500 mg/l (equivalent to an 8-hour TWA styrene exposure of about 80 ppm).

Conversely, mutagenic activity has not been found in most *in vitro* tests of styrene. This has been the case with *S. typhimurium* [172,173,174,176], *E. coli* [174], the yeasts *S. pombe* and *S. cerevisiae* [175], and cultured Chinese hamster cells [175,176]. However, a few studies [171,177,178] have found weak evidence of the mutagenicity of styrene in *S. typhimurium*.

A dose-response relationship has been shown in the induction of sister chromatid exchanges in human whole blood lymphocyte cultures treated with styrene [181]. In a study of unscheduled DNA synthesis in lymphocytes of styrene-exposed workers, styrene did not alter the efficiency of DNA repair but rather predisposed the lymphocytes to an increased risk for DNA damage from subsequent exposures to genotoxic agents [137]. Some studies in lower

mammals suggest mutagenicity by styrene while others suggest otherwise. In vitro studies, such as the Ames tests, tentatively suggest that styrene is not mutagenic. Clearly, these conflicts in the data on the mutagenicity of styrene need to be resolved. These same tests, on the other hand, uniformly show styrene oxide to be mutagenic. Styrene oxide, also known as styrene epoxide, has been proposed [224,225] as an intermediate in the metabolism of styrene, but it has not been found in vivo. The ability of epoxides to react with nucleic acids, and possibly lead to germinal or somatic mutations, is a major concern in the question of intermediary metabolism of styrene. Whether styrene oxide (if formed) is present long enough to bind covalently to genetic material or other macro molecules is not known. Airborne styrene oxide is present in some workplaces, apparently those in which peroxides and styrene are mixed [233,269]. While the toxicity of styrene oxide has not been adequately studied, it is mutagenic and carcinogenic. Its health significance in these workplaces needs evaluation both in terms of its own toxicity and possible toxic interactions with styrene and other chemical substances.

There have been a few reports of defects in children born to women exposed to styrene [66], but this implication of teratogenesis has not been confirmed by experimental animal studies [190,191,192,193]. It has been demonstrated, however, that styrene can cross the rat placenta and that styrene concentrations in fetal blood are almost as high as in maternal blood [189]. Styrene can also cross the human placenta, as demonstrated by the fact that styrene was found in umbilical cords [65].

An increased incidence of spontaneous abortions among Finnish styrene workers has been reported [139]. However, the study involved only six cases, and the investigators [139] were not able to control for smoking or economic status (two variables that are risk factors in spontaneous abortions). In 1982, the same Finnish investigators [140] reported that 67 female RP/C workers, prior to the period of exposure, had no significant differences in their reproductive outcomes as compared to controls, matched for age and social class, with no solvent exposures. During styrene exposure the numbers of pregnancies were not significantly different, but there were significantly fewer births among the RP/C workers (4 vs. 14); one cause was an increased (although not significantly) number of induced abortions (8 vs. 4). The number of spontaneous abortions was identical with four in the exposed group and four in the control group. Suggestions that styrene is teratogenic and abortifacient need to be pursued, but resolution will be difficult because of the problems typically associated with attempts to relate human defects to causal factors. However, the findings presented above provide strong rationale for an investigative program, including appropriate recordkeeping and registries, to develop etiological information on birth defects and abortions associated with occupational exposures.

There seems to be little basis from experimental animal investigations or epidemiological studies to conclude at this time that styrene is carcinogenic. Two animal studies [196,197] reported an increased incidence of lung tumors, but not consistently either in one sex or in one

species. Another animal study [195] reported an elevation (not statistically significant) in the combined incidence of leukemia and lymphoma. Existing mortality studies [31,78,83,84,142] have shown no relationship between styrene exposure and an excess in the incidence of deaths in the overall category, "All Malignant Neoplasms." However, excesses of deaths were reported in the specific cancer categories "Lymphatic and Hematopoietic, except Leukemia" (7 observed vs. 5.3 expected, not significantly different) and "Leukemia" (6 observed vs. 3.4 expected, not significantly different) in the study by Ott et al. [31]. While the evidence developed so far concerning the carcinogenicity of styrene is not conclusive, it does provide sufficient bases for carefully considering to what extent workers are exposed to styrene and for instituting controls to reduce those exposures. The recommendation of NCI [197] for additional animal experimentation to add more evidence because of deficiencies in present data seems the most appropriate recommendation that can be made now. Two factors warrant a high priority for investigations to help resolve this important issue: the commercial importance of styrene and the large population that is exposed to the compound.

The experimental evidence [69,70,72] for styrene-induced health effects at a concentration of 100 ppm is not strong; however, there are many clinical studies showing similar, as well as other, adverse health effects in occupational settings. Although these workers also had potential exposures to other substances, their major exposure was to styrene. Additionally, in some of the studies, peak and TWA styrene exposures may sometimes have exceeded 100 ppm, but exposures for most workers were judged to be at TWA styrene concentrations at about 100 ppm [76,81,82,84,91,94,106, 109,110,111,112,113,115,118,120,124,129,130,131,132,138,392]. CNS effects noted in those workers exposed to styrene at or below 100 ppm included subjective complaints such as fatigue, dizziness, headache, nausea, poor memory, and drowsiness [106,109,110,112,113,138]; increased reaction times [111,392]; abnormal EEGs [106,118,124]; and impaired balance [106]. Chromosomal changes were also more frequent in the lymphocytes of styrene-exposed workers in several RP/C factories with TWA exposures of about 100 ppm than among controls [76,129,130,131,132].

Based on the adverse health effects demonstrated in experimental subjects and workers exposed to styrene concentrations at and below 100 ppm, a TWA exposure limit of 50 ppm is proposed over the workshift for up to a 10-hour workday and a 40-hour workweek. This recommendation is further supported by studies showing effects such as slower reactions [72], subjective complaints related to CNS depression [72], and abnormal EEGs [124] at styrene concentrations around 50 ppm.

A ceiling limit of 100 ppm based on a 15-minute sampling period is recommended to prevent acute irritation effects on the eyes and upper respiratory system. Since styrene is a defatting agent and can cause primary skin irritation [234] and dermatitis [54,56,61,91,104,113,

122,126] in workers, as well as be absorbed percutaneously [86,151,152], skin contact with styrene should be avoided through the use of good work practices and personal protective clothing.

Other toxic effects such as peripheral neuropathy, abnormal pulmonary function, liver toxicity, mutagenicity, teratogenicity, and carcinogenicity would be relevant to an occupational exposure limit if the available information established them as effects of styrene exposure or gave information on exposure-response relationships. These health effects need further investigation and would provide additional evidence for a reduction in the current occupational exposure standard if they were found to be styrene-related.

VIII. METHODS OF WORKER PROTECTION

Informing Workers of the Hazards of Styrene

Each worker with potential exposure to styrene should be informed of (1) relevant prenarcotic symptoms, (2) effects of overexposure, including suspected but as yet unproven effects, (3) proper use and handling of styrene, (4) methods that minimize exposure, (5) proper maintenance procedures and cleanup methods, (6) correct use of protective clothing and equipment, including respiratory devices, (7) engineering controls in use or being planned to limit exposures, and (8) medical and environmental monitoring procedures in use. The advantages to the worker of participating in the monitoring procedures should be stressed. Oral as well as written instructions informing workers of proper handling methods, cleanup and emergency procedures, use of personal protective equipment, etc. should be presented by persons qualified by experience or training in occupational safety and health as part of a continuing education program. The NIOSH publication A Recommended Standard--An Identification System for Occupationally Hazardous Materials [306] should be used as a guide when preparing written material for readily available reference on the relevant physical, chemical, and toxicological properties of styrene or of mixtures or formulations containing the compound. Required information shall be recorded on the "Material Safety Data Sheet" shown in Appendix III, or on a similar form approved by OSHA, U.S. Department of Labor. Pertinent information on over 1,300 substances may be found in the Hazardous Chemicals Data Book [307] or other similar references.

Workers should also be instructed on their responsibilities for proper work practices and sanitation procedures to help protect the health and safety of themselves and their fellow workers.

Work Practices

(a) Storage, Handling, and Transportation

Because of the volatile and flammable nature of styrene (see Table III-1, p. 17), proper handling and storage should be given special attention. Good ventilation systems with explosion-proof motors are necessary in areas where styrene is handled and stored. Grounding of all equipment, tank cars and trucks, and hose connections will discharge static electricity. An inlet line that discharges at or near the bottom of the tank and makes electrical contact with the tank will eliminate uncontrolled electrical discharges [308]. If the inlet line cannot reach the tank bottom, a chain should be attached that does reach [309].

Precautions to ensure that styrene vapor does not ignite are mandatory for safe conditions, especially at elevated temperatures. Recommendations

include: (1) regular inspection of equipment and storage tanks, (2) immediate repair of leaks, pumps, and lines, (3) ventilation to reduce vapor concentrations, (4) use of special nonsparking alloy tools, (5) periodic tests of pressure equipment, (6) rapid removal of spills, and (7) elimination of ignition sources [309]. Portable electric lights and power tools must conform with the National Electrical Code, Article 500 [310]. Receptacles that contain styrene monomer or hot styrene-containing resins must be tightly covered at all times except when material is removed. Safety cans can be used to hold working amounts of liquid styrene.

Styrene may polymerize if it comes in contact with oxidizing agents and catalysts such as peroxides, strong acids (e.g., sulfuric or hydrochloric), aluminum trichloride, phosphoric anhydride, and iron chloride. Storage of styrene away from oxidizing agents, catalysts, and strong acids will also help prevent explosions or fires. Centrifugal pumps will cause polymerization if allowed to run with a closed discharge line. Storage of styrene outdoors or in detached areas can be advantageous [311].

If styrene is stored more than 30 days at 90°F (about 32°C) or above, the inhibitor concentration must be checked at least bi-weekly [312]. Styrene storage containers can be installed with a temperature alarm system to signal interior temperature increases that may result in runaway polymerization, a special concern in hot climates [309,313]. The rate of polymer formation in storage tanks can be reduced by cooling the tank by means of a water spray, refrigeration, insulation, or reflective painting [313].

Catalysts, promoters, and accelerators should be stored in cool, dry, dark areas away from reducing agents, and in their original shipping containers [314]. Fuller and Jensen [314] also suggested that only a 1-day supply of peroxides be kept in laminating areas. (As was discussed in Chapter V, styrene and peroxides can possibly react to form another toxic compound, styrene oxide.)

(1) Drums

Unless drums are unloaded carefully, they may be damaged; dropping or bumping drums can lead to leaks or ruptures. Examination of each shipment for leaks can identify those drums that need special handling. If any are found, spillage can be minimized by turning the leaking part up while they are being moved to a safe place to stop the leak or by transferring the contents.

Containers that have held styrene monomer must be thoroughly cleaned with steam and then drained and dried before reuse, because small amounts of the monomer may remain and present a fire hazard. Explosions can occur if drums are not filled and emptied carefully as demonstrated in a report by the Manufacturing Chemists Association [315]. A supposedly empty drum was placed over a steam line so that the drum could be cleaned. The residual styrene ignited (probably due to a discharge of static electricity

between the nozzle of the steam line and the drum) and then exploded. Drums cleaned by steam should be electrically bonded to the steam lines and the entire assembly grounded.

A similar accident occurred [316] when a worker who was filling drums with styrene failed to ensure that the drums were properly grounded. While the last drum was being filled, the worker moved it; a spark discharged between the filling line and the drum, causing an explosion.

Before drums are emptied they should be supported and blocked to prevent movement. When filling open containers from a drum, electrical bonding must be provided to prevent static sparks. Styrene workers should avoid striking fittings with tools or other hard objects that may cause sparks. The National Fire Protection Association (NFPA) Standard No. 77, "Static Electricity" [317], contains detailed information on the subject.

During lay-up operations in the reinforced plastics industry, it is recommended that all styrene monomer be kept in safety cans, rather than in large open containers, to prevent high local styrene concentrations.

(2) Tank Trucks and Cars

Fire hazards around tank trucks and cars can be reduced by turning off truck motors and not starting them while tank trucks are being loaded or unloaded. If tank trucks and cars are unloaded through an open dome, the unloading equipment must be electrically bonded and grounded before operations are started. Use of a rubber-type flexible hose to unload styrene is not recommended because it may not be resistant to styrene. Fluoroelastomer hoses, however, are satisfactory because they are more resistant to styrene penetration [308].

There are other hazards involved in transferring styrene from or to tanks that should be identified, so that workers can be instructed on appropriate precautions. This is exemplified in the case of one worker who, after unloading styrene from a tank car [315], disconnected a supposedly empty line that was, in fact, filled with styrene. The styrene spilled on his face and shoulders; although he was wearing safety glasses and a hard hat, the styrene ran down his forehead and into his eyes. Details regarding the extent of his injuries were not provided. After this accident, rubber gloves and goggles were worn by personnel who unloaded tank cars, and written guidelines were provided that detailed safe procedures for unloading tank cars [315].

Department of Transportation (DOT) regulations that apply to the handling, unloading, and transportation of hazardous substances are set forth in 49 CFR 100-199.

(3) Return and Disposal Precautions for Styrene Containers

Extra care in completely draining the contents and properly closing all openings before shipping containers are returned to suppliers will help prevent explosion and fire. As soon as a tank car or truck is completely unloaded, all valves must be closed tightly, the unloading connection removed, and all other closures made tight, except the heater coil inlet and outlet pipes (if any), which must be left open for drainage.

(b) Sanitation and Hygiene

In the interest of good hygiene and to prevent accidental ingestion of styrene, it is important that storing, handling, dispensing, and eating of food be prohibited in all areas where styrene is kept or used. It is also important that workers who handle styrene wash their hands thoroughly before eating, smoking, or using toilet facilities. Workers should also be provided with facilities so they can shower with soap and water at the end of each workshift, or as soon thereafter as practicable before leaving work. Facilities such as double lockers should be provided for workers so soiled clothing can be stored separately from clean clothing.

Clothing that has become saturated with styrene must be removed immediately because styrene is absorbed through the skin [151,152,153]. Because skin absorption can occur, contaminated skin must be promptly washed with soap and water. Use of acetone or other organic solvents to clean styrene from the skin can be harmful since they may be toxic themselves and contribute to the effects of styrene. In case of eye contact, flush the eyes immediately with a copious flow of water for 15 minutes to prevent corneal injury. If irritation persists, get medical attention. Eye contact can be prevented if workers wear splash-proof safety goggles or face shields that comply with 29 CFR 1910.133(a).

(c) Housekeeping

Good industrial housekeeping is imperative to prevent fires or accidental ingestion where styrene is used. Vacuuming of work areas at the end of each shift to remove particulate matter such as polymer dust, fibrous glass, and fibrous glass-reinforced plastic dust is a simple and effective measure.

Styrene spills should be cleaned up immediately after eliminating potential sources of ignition and using available ventilation. Stopping leaks and spills will also eliminate fire hazards and help conserve raw materials, keep chemicals out of the effluent system, and reduce worker exposure [32]. Vermiculite, dry sand, earth, or similar nonreactive material can be used to absorb styrene but, for best results, pretest absorbing agents for their effect on polymerization of styrene. For spills on hard surfaces, scrubbing the area with soap and water after most of the styrene has been removed is recommended. If spills occur in a confined space, pumping water into the area will prevent the ground from absorbing

the styrene and may allow styrene to be recovered later [318]. Small spills can be absorbed by paper, which can be burned after evaporation in a hood or in another safe place. Only properly protected personnel should perform these procedures. Wiping rags or cloths should be placed in fireproof receptacles equipped with tight-fitting lids.

(d) Waste Disposal

Because of the exothermic nature of styrene polymerization, it is recommended that waste catalyst be disposed of separately from waste monomer. If this is not possible, the waste receptacle should be located away from any sources of heat, flame, or electrical discharge, or from any combustible material. Besides cleaning work areas at the end of each workshift, it is a good practice to determine if all wiping cloth containers, excess plastic, plastic constituents, and other refuse are removed from the building and disposed of properly. Workers should be informed of proper storage and disposal procedures and be adequately supervised in handling waste receptacles.

All waste styrene and styrene-contaminated material should be removed to a disposal area and safely burned by introducing it as a spray or mist into a suitable combustion chamber; incineration will be more complete if styrene is mixed with a more flammable solvent [314]. Water contaminated by styrene can be safely treated by removing the mixture to a safe location and blowing it with air. The outlet air stream can then be burned to remove the styrene [308]. Waste effluent gases can also be burned to remove styrene [319]. Liquid styrene should not be allowed to enter a confined space, such as a sewer, because of the possibility of an explosion, at least in warm or hot areas.

(e) Fire Control

Styrene poses a significant fire hazard. As shown in Table III-1 (see p. 17), styrene has a boiling point of 145.2°C (293.4°F), a flashpoint of 34° to 37°C (94° to 98°F), and flammable (explosive) limits of 1.1-6.1% by volume in air. Thus, according to the criteria of OSHA, styrene would be classified as a Class 1C flammable liquid (29 CFR 1910.106) and a Class B fire hazard (29 CFR 1910.156).

If ventilation is adequate to maintain the concentration of styrene at recommended levels, the potential for fire and explosion will be greatly reduced. However, elevated styrene concentrations may occur if the vapor accumulates, for example, above the liquid surface, in depressions, at container openings, at vent openings, or in areas having poor ventilation. Thus, all ignition sources, such as fire, sparks, and smoking materials, must be prohibited in those areas where styrene is made, used, or stored. NFPA Standard No. 77, "Static Electricity" [317], lists precautions designed to prevent the accumulation of static electricity, a potential ignition source. Fifty feet from open flames or other possible ignition sources, such as sparks, hot surfaces, or arcs, has been suggested as the

minimum safe distance for location of processes that involve styrene [314]. Fire hazards can also be reduced by isolating mixing and formulating operations from other operations (particularly laminating areas) in a well-ventilated area equipped with an automatic sprinkler system; mixing, formulating and laminating operations should also be separated from finishing areas by at least 2-hour fire partitions to slow the spread of a fire [314].

Some processes do not lend themselves to control by physical separation. This is especially true when the contaminant permeates an entire work area. In those cases, either isolation or enclosure of the operation will limit the amount of contaminant dispersed in the workplace [90].

Fires involving styrene can be safely extinguished with the proper use of foam, dry powder, or carbon dioxide. Water is not an effective extinguishing agent but can be used to keep fire-exposed containers cool. Regulations governing the use of electrical equipment where styrene is present can be found in the National Electrical Code NFPA 70-1971, ANSI CI-1971 (Rev. of C1-1968) which was adopted as a national concensus standard by OSHA in 29 CFR 1910.308.

Incomplete combustion of styrene-containing materials may result in the formation of a toxic gas such as carbon monoxide; the breathing of fumes, smoke, and gas liberated by styrene, polystyrene, or other styrene-containing materials [309,318] can be avoided by using the appropriate respiratory protection.

Fuller and Jensen [314] suggested that sprinkler systems be installed in new factories where reinforced plastics are laminated. They recommended that these systems deliver a minimum of 0.3 gallons of water/min/sq ft (3.7 liters/min/sq m) applied over an area of 5,000 sq ft (464 sq m), that the sprinkler system be provided with hand hose connections, and that portable Class B fire extinguishers also be available [314].

To help control potential fires, Fuller and Jensen [314] suggested that smoke and heat vents be installed with about 100 feet (30.5 m) between their centers. They also suggested that curtain boards be installed at 100-foot intervals so that curtained areas are no greater than 10,000 square feet (929 sq m).

(f) Entry into Confined Spaces

Entry into confined spaces (tanks, pits, tank cars, barges, process vessels, and tunnels) should be controlled by a permit system or other program offering equal protection. These spaces need to be tested for oxygen deficiency, styrene concentration, and the presence of any other harmful gas or vapor. Only supplied-air hoods or suits impervious to styrene are recommended for entering a confined space unless sampling data indicate that the area is safe for entry with other equipment. Air- or

oxygen-supplied masks equipped with full facepieces are recommended to be worn when the oxygen content of the air is less than 16% or when the styrene vapor concentration is over 5,000 ppm.

It is imperative that confined spaces be thoroughly ventilated and cleaned before workers enter without respiratory protection. It is a good practice to flush the confined space with steam or water to remove styrene vapor. When a worker enters a confined space, use of a safety line is recommended with another properly protected worker on standby outside to maintain communication by voice and sight with the worker inside. The safety line must never be abandoned while the worker is in a confined space. An additional safety measure is to have the workers in or near to the confined space close to others who can be quickly contacted in an emergency [308]. The NIOSH document Working in Confined Spaces [320] contains a more thorough discussion on the subject of confined spaces.

A number of effective work procedures and housekeeping practices in the RP/C industry were noted during a 1981 NIOSH-sponsored study on worker education, training, and motivation [321].

Engineering Controls

Engineering controls for production and use of styrene are designed in consideration of its volatility, flammability, and toxicity. Styrene undergoes rapid, exothermic polymerization. If unchecked, this reaction can become violent and ignite or explode [322]. Fuller and Jensen [314] reported that one such incident occurred in 1971 in a plastics manufacturing plant in Ohio. To avoid this problem, continuous monitoring of the temperature and pressure of liquid styrene storage tanks can be used to alert workers of any temperature or pressure increase that would indicate polymerization.

The following control principles and methods are pertinent to all processes used for the production of styrene, polystyrene, reinforced plastics, synthetic rubber, and other styrene-based plastics. The methods of control include process isolation, process containment, and ventilation.

(a) Isolation of Incompatible Processes

The physical isolation of incompatible processes is sometimes required to achieve a safe work environment. For example, styrene readily reacts with low concentrations of halogens in the presence of ultraviolet light to form a potent lacrimator [323], a problem that can be prevented by isolating processes that generate halogens from processes that use or make styrene. In the reinforced plastics industry, the separation of grinding and sanding operations and fibrous glass cloth cutting areas from areas where styrene is being used has been recommended to reduce dermatitis [324].

(b) Containment

Closed process systems are the best way of preventing worker exposure to styrene; where practical, closed systems with negative pressure inside are preferred. Even with the use of closed systems, contact with styrene may still occur at pump seals and sampling ports, during draining, filling, and cleaning processes, and at spills. Unreacted styrene may be recycled to separate it from the polymerized product by vacuum devices. Closed loop sampling devices help minimize worker exposure [32]. For these systems to be effective, proper operation, maintenance, and frequent testing for leaks or other malfunctions are necessary. Use of remote control and automated processes can also reduce exposure to styrene.

(c) Ventilation

When closed process systems are not possible, exhaust ventilation, preferably local exhaust ventilation, may be needed to limit exposures to styrene. Because of fire hazards, ventilation systems need nonsparking fans and ducts. In addition, ventilation systems should prevent the recirculation of contaminated air. The ease of periodic inspection and cleaning are necessary considerations in proper design and location of valves, vents, gauges, pressure-relief devices, and other engineering controls. This is very important because styrene can easily polymerize and block vents or prevent valves, gauges, and pressure-relief devices from functioning properly [308].

(1) Local Exhaust Ventilation

Well-designed local exhaust systems can be used to effectively control styrene vapor, particularly during such work as spray-up, lay-up, and open molding operations where high concentrations of styrene are often encountered. Intensive local ventilation has been recommended as the only practical method of reducing styrene vapor concentrations during the construction of large reinforced plastic objects [324].

During the production of synthetic rubber, a large amount of styrene may be vaporized and released during drying operations, which are usually performed at elevated temperatures and are open to the atmosphere. Mallette [54] recommended that dryers be operated with a slight negative pressure or, if this was not feasible, that exhaust hoods be installed at the dryer outlets to regulate the escape of styrene vapor. When local exhaust systems are not feasible, area fans may have to be used to direct vapors away from the workers.

(2) Dilution Ventilation

When the concentration of the contaminant cannot be reduced at its source, other methods are necessary. One method controls the concentration in the general work environment by using general dilution ventilation, a method which is not usually as satisfactory as local exhaust ventilation.

Data such as the evaporation rate, temperature, and the surface area of the source of the contaminant, together with information on the toxicity of the contaminant, are needed to design an efficient dilution ventilation system [325]. To help reduce the risk of fires in the reinforced plastics industry, Fuller and Jensen [314] recommended use of a general ventilation system with an air flow of 1 cu ft/min/sq ft of floor space.

When ventilation is used to control exposure, it is desirable to have trained personnel make measurements that demonstrate system efficiency (i.e., velocity pressure, static pressure, or total pressure) on a periodic schedule as determined by a qualified industrial hygienist. It is also a good practice to measure system efficiency when there is any change in production, process, or control method. This necessitates maintenance of records that demonstrate the effectiveness of such changes; information needed includes date, type, and location of test, and results of the measurements taken.

(d) Other Control Methods

The difficulties in limiting exposures of workers to styrene and other materials in RP/C operations by conventional methods such as local exhaust ventilation or closed processes have motivated development of other approaches. Several of those attempts are described below.

In 1971, Maisonneuve and Lardeux [326] described a ventilation scheme that could be used in the construction of reinforced plastic boats. They suggested that the boat form should be mounted on wheels and be made so that it could rotate on its axis to facilitate work on both sides from one position. They also suggested that the boats (6.5 m long in this case) be constructed in a room that was 8 m long and had a fresh air stream with a flow of 0.5 m/s (about 100 ft/min). This air stream should be supplied across the entire length of the room, particularly at worker breathing zones. The investigators [326] also described various ventilation systems designed to reduce a worker's exposure to styrene during production of boats made from reinforced plastics.

In 1980, Willis [327] described some of the problems in trying to reduce styrene emissions during the curing process in boat building. An attempt to reduce styrene emissions by decreasing gel time was unsuccessful because the method used to decrease gel time involved increasing the workshop temperature to a high level. This halved the cure time but increased the amount of styrene evaporated to three times normal. Low-styrene emission (LSE) resins (also known as environmental resins) were tried several years ago, but there were disadvantages with the first resins tried. At first, addition of paraffin wax to the resin was thought likely to produce a screen between the resin and the air; however, the wax did not rise to the surface soon enough, and the wax impaired interlaminar adhesion. Other resins have subsequently been developed, but their nature, other than that some act to increase surface tension, was not described; apparently, their formulation or exact nature is proprietary.

LSE resins are now available, according to undocumented statements by Willis [327], that do not inhibit interlaminar adhesion, and claims for reduction of emissions of as much as 95% have been made. It was emphasized that use of these resins did not preclude the necessity for proper ventilation, but it was said that their use reduced the amount of ventilation needed, and assisted in reducing airborne concentrations of styrene.

In 1980, a group of representatives from the RP/C industry in the U.S. visited Sweden to assess Swedish technology in reducing styrene emissions and its applicability to U.S. operations. Their unpublished report [328] was furnished to NIOSH by The Society of the Plastics Industry, Inc. Only plants manufacturing small boats (up to 30 feet in length) were visited; these shops utilized hand lay-up/spray-up operations. The visiting group concluded that, in these small boat plants, engineering controls alone were not sufficient to achieve the occupational environmental limit in force at the time (i.e., 40 ppm), but that compliance could be achieved through a combination of high volume, low velocity air movement, use of personal protective equipment, different plant layouts, proper work practices, and environmental resins. Moreover, plant layouts needed to help achieve these reduced emissions were judged to result in productivity lower than that found in U.S. plants. It seemed doubtful to the study team that the 60 ppm ceiling limit was being met. (Verification of such a ceiling limit has not been found in other sources, including an official Swedish listing [329].) It was noted that there were no styrene emission standards in Sweden, so styrene could be exhausted directly outside the plant.

Other Swedish control systems found useful, in addition to ventilation, were the use of airless spray guns, and the bulk storage of resins underground which were piped directly to the spray guns. Specially designed cutting and grinding tools reduced dust exposure. In one boat plant, the spray booths had movable curtain walls that could completely surround the object being fabricated. In all cases, the inlet to the booths was constricted in some manner. Swedish experiments had indicated that an air velocity of 0.5 m/s was necessary to achieve 40 ppm, and 0.8 m/s to achieve 25 ppm. This air was introduced through diffusion filters. Elephant trunk hoses were placed at strategic locations around styrene sources for the purpose of exhausting the air. Dust emissions were exhausted through tool-mounted vacuum systems [328].

The Swedish workers were well trained, and followed proper practices well; work practices were reinforced by management attitudes. Workers were rotated so that only about half of their time was spent on spraying or rolling. During spraying, workers wore full head coverings, charcoal respirators, ear protection, and full-face plastic shields. Management of the Swedish boat plants felt that these protective items were not needed [328].

Initial LSE (environmental) resins, put into use in Sweden in early 1977, posed delamination problems, but these were eliminated in the second

generation resins introduced about a year later. In addition to resulting in reduced styrene emissions, these resins result in a surface that is less tacky, thereby reducing the potential for dust accumulation with consequent lamination problems [328]. One Swedish firm installed strips of fibrous glass screen in areas where further lamination to stringers or bulkheads was expected. It was installed in the final application of wet resin, then peeled off just before the stringer or bulkhead was installed, revealing a clean surface for lamination.

The nature of the environmental resins was not described in the Swedish report [328], although several European purchase sources were listed; this reinforces the inference made earlier that these resins are proprietary in nature.

A 1980 report [330] gave drawings and some specifications for a number of types of hoods, canopies, and ducts, with exhaust air quantities and velocities and other general information, recommended for use in various RP/C operations. These were described as hardware either currently in use or available for use to control styrene emissions in RP/C operations. Efficacy data, for example, data regarding what the airborne emissions were, or how much of a reduction in air emissions could be or was achieved, were not reported.

As was indicated in Chapter V, airborne styrene oxide may be found in reinforced plastics operations. While the concentrations reported in limited studies [233,269] have been low, they may nevertheless be toxicologically significant.

When worker exposure cannot be adequately controlled by engineering controls, protective clothing and equipment, including respirators, may be needed. These are controls of last choice because of the difficulty of program management, which includes selecting and maintaining equipment and instructing workers on proper use and fitting, and worker acceptance and efficiency. Thus, neither respiratory protective equipment nor personal protective clothing is an acceptable substitute for proper engineering controls.

More detailed information on industrial ventilation can be found in publications of the American National Standards Institute (ANSI) [331], the American Conference of Governmental Industrial Hygienists (ACGIH) [325], and NIOSH [332]. Other NIOSH publications [333,334] give details of engineering control technology in use in the plastics and resins industry.

Personal Protective Clothing and Equipment

There have been several reports of skin irritation caused by styrene [2,54,56,61,91,104,113,122,126]. Blistering of the skin with loss of hair occurred when liquid styrene was applied repeatedly to the ear of a rabbit, and marked irritation with necrosis was found with two applications

of liquid styrene to the shaved abdomens of rabbits [53,162]. Liquid styrene has been shown to be absorbed through the skin of both humans [151] and animals [165]. It was estimated that exposure of the palms of both hands to liquid styrene for 90 seconds would result in an absorption of styrene equivalent to the inhalation dose during a day of work at about 12 ppm [151].

Where workers may come in contact with liquid styrene, the use of appropriate equipment such as impervious gloves, boots, overshoes, bib-type aprons (at least knee length), face shields with goggles, and appropriate protective clothing is recommended. Proper selection of protective equipment is also necessary. For example, neoprene gloves and boots deteriorate rapidly and give protection for only a short time [32]. Leather shoes also do not provide adequate protection against liquid styrene [308,318]. Polyvinyl alcohol and polyethylene are reported to provide good protection against styrene [335].

Dermal contact may be a particular problem in those shops where styrene is poured, spread by hand, and sprayed. It is during the use of these techniques that the greatest airborne concentrations of styrene should also be expected. Thus, any worker who performs these operations or is near them while they are being performed should be provided with protective clothing and eye protection that will prevent skin and eye contact with styrene. These precautions should also be taken when workers enter an area where a leak or spill has occurred. Suitable pre-tested respiratory protective devices should also be made available to the worker.

Although barrier creams have been suggested as a beneficial method of preventing skin irritation [102], it has not been demonstrated that barrier creams are sufficiently impermeable to prevent absorption of styrene and dermal irritation. It is also possible that barrier creams may hold styrene in contact with skin and thereby increase irritation and penetration.

Styrene vapor can also penetrate the skin [154]. Thus, when work is being performed in areas where there are high concentrations of styrene, such as some confined space work, protective clothing as well as respiratory protection may be needed to prevent undue absorption.

In 1971, Bagdinov [336] reported that styrene vapor does not diffuse through certain protective textiles until the vapor concentration is greater than 5 ppm. In a comparison of the protective properties of various textiles, the least diffusion was through a mixture of wool and polyacrylonitrile . The effects of body movements that might force air through the fabric faster than it could diffuse were not considered.

While inside protective gloves, the hands may perspire. This problem can be minimized by wearing white cotton inner liners and making replacement liners available [337].

Workers exposed to styrene have experienced eye or nasal irritation or, usually, both [35,53,56,58,59,61,93,104,110,113,114,115,126]. To prevent eye irritation at moderately low concentrations, full-facepiece rather than half-facepiece respirators are recommended whenever work must proceed in areas where styrene concentrations are excessive.

If a worker complains of eye irritation from styrene while wearing an approved full-facepiece respirator, poor fit or sorbent exhaustion may be the cause [338]. Chemical cartridge respirators provide respiratory protection for relatively short periods. Respirators currently available do not contain an end-of-service-life indicator for styrene; therefore, the user must follow the manufacturer's recommendations for changing canisters or cartridges.

Although many workers may become accustomed to the irritancy of styrene vapor, systemic effects may still occur. Therefore, it is important that the employer follow the manufacturer's directions for changing canisters or cartridges on a regular schedule and not rely on worker complaints of irritation as an end-of-service-life indicator for respirators.

The type and class of respiratory device to use (see Table I-1, p. 8) is determined by taking atmospheric samples in the work areas and then selecting the appropriate device according to guidance on respirator selection. Routine sampling, as well as sampling after control, process, or climatic changes is recommended. Approved full-facepiece respiratory protection is desirable if the worker is exposed concurrently to styrene and benzene, toluene, or ethylbenzene, because simultaneous exposures to styrene and one or more of these other solvents may cause a decrease in the rate of metabolism of styrene, according to an experimental study [218]. Such exposure should be avoided whenever possible.

Regulations concerning personal protective equipment and respiratory protection can be found in 29 CFR 1910.133, 29 CFR 1910.134, and 30 CFR 11. NIOSH test data and recommendations for eye protection, which comply with ANSI Z87.1, can be found in two NIOSH publications [339,340].

Exposure Monitoring and Recordkeeping

To characterize worker exposures, the employer should conduct personal sampling and analysis for styrene. Estimates of the exposure of each worker should be made, whether or not each worker's exposure is measured by a personal sampler. Thus, a sampling strategy that allows reasonable estimates of each worker's exposure should be used. Records of such monitoring should include sampling and analytical methods, times and locations of samples, whether protective devices (especially respiratory protective devices) were in use, and the concentrations found or estimated. It is important, in the case of estimated concentrations, that information on which the estimates were based be included.

It is also important that pertinent medical records (i.e., results of medical examinations, the physician's written opinion, medical complaints, medical and work histories, etc.) be established and maintained for all workers, and that copies of any environmental monitoring data applicable to the worker be included in these records. To ensure that they will be available for future reference and correlation, they should be maintained for the duration of employment plus a period of 30 years. Copies of these medical and environmental records should be made available to the worker, former worker, or to his or her designated representative following specific written consent of the worker. In addition, the designated representatives of the Secretary of Health and Human Services and the Secretary of Labor should have access to the records or to copies of them.

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X. APPENDIX I

METHOD FOR SAMPLING AND ANALYSIS OF STYRENE IN AIR

General Requirements for Styrene Air Sampling

Air samples are collected that represent the air a worker breathes while performing each job or specific operation. It is advisable to maintain records of the date, time, rate, duration, volume, and location of sampling. It is also advisable to record the temperature, pressure, and relative humidity at the time the sample was taken, as well as other pertinent information.

Sampling

(a) Sampling Strategy and Apparatus

Air samples are collected as near to the worker's breathing zone as practicable, but without interfering with the worker's freedom of movement. These air samples are collected in a manner that will allow the determination of the worker's exposure for every job he or she performs where styrene is used. It is recommended that a number of air samples be collected so that the variability of exposures throughout the work area can be determined. Statistical sampling strategies are given in the NIOSH publication Occupational Exposure Sampling Strategy Manual [341].

To collect these air samples on charcoal tubes, battery-operated pumps are needed that have clips for attachment to the worker's clothes. It is necessary that these pumps be capable of calibration within 5% at operational flow-rates.

The analytical method as described later in this appendix is for samples collected by use of glass tubes, 7 cm long, with an outside diameter of 6 mm and an inside diameter of 4 mm. These tubes contain two sections of 20/40 mesh activated coconut-shell charcoal that was fired at 600°C. The first section is the adsorbing section and contains 100 mg of charcoal. The second, or reserve (backup) section, contains 50 mg of charcoal. The sections are separated by 2 mm of urethane foam, with 3 mm of urethane foam placed between the reserve section and the end of the tube; a plug of silylated glass wool is placed between the other end of the tube and the adsorbing section. Tubes that contain larger amounts of charcoal are also available. Such tubes may be used if results obtained using the standard size tubes indicate that breakthrough has occurred or if substantial amounts of organic compounds that may interfere with styrene collection are also known to be present. The pressure drop across the tube must be less than 1 inch of mercury at a flow-rate of 1 liter/min. Tubes that meet the specifications described above are commercially available.

(b) Calibration of Sampling Instruments

Air sampling instruments should be calibrated at operational flow-rates with a representative charcoal tube in line. Positive-displacement diaphragm pumps require accurate determination of the stroke factor. In addition, pumps must be recalibrated after any repair to, or modification of, the sampling system is made. It is also necessary to spot check the volumetric flow-rate through the sampling system and to make adjustments before and during each study to ensure accurate airflow data.

(c) Collection and Handling of Samples

The following steps are recommended for the proper collection and handling of air samples:

(1) Immediately before sampling the air, both ends of the charcoal tube are scored and broken so that openings of at least one-half the 4-mm internal diameter of the tube are made.

(2) The smaller, or reserve, section of charcoal is positioned toward the sampling pump.

(3) The charcoal tube is placed in a vertical position during sampling to prevent channeling and consequent sample loss.

(4) The air sample is drawn directly through the adsorbing section of charcoal without first passing it through any tubing; tubing may be used to connect the back of the tube to the pump.

5) Sampling at 1 liter/min for 15 minutes should provide an adequate sample for measuring ceiling concentrations. A sampling rate of 250 ml/min is recommended for measuring TWA exposures over an entire shift.

(6) Immediately after sampling, the charcoal tubes are sealed with plastic caps that are inert to, and contain no styrene. Under no circumstances should rubber caps be used.

(7) Prepare a charcoal tube to serve as an analytical blank. No air is drawn through this tube, but it is broken, sealed, and, if appropriate, transported in the same way as the charcoal tubes that were used to collect the sample.

(8) If tubes are to be shipped it is necessary to ensure that they are packed tightly and well padded to prevent breakage.

(9) A sample of the bulk styrene used in the facility where the air has been sampled should be submitted to the laboratory in a glass container sealed with a Teflon-lined cap. This sample should not be transported in the same container as the charcoal tubes.

Principle of the Method of Styrene Analysis

A measured volume of air is drawn through a charcoal tube to adsorb airborne styrene onto the charcoal. The adsorbed styrene is subsequently desorbed from the charcoal with carbon disulfide. A suitable portion of the desorbed sample is subjected to gas chromatography, and the amount of styrene is determined by comparing the area under the styrene peak with a standard curve that relates peak areas to the concentration of a known standard.

Range, Sensitivity, Precision, and Accuracy

(a) Although the lower detection limit of the method [259] has not been determined for styrene, a sample volume of 10 liters is considered adequate for measuring styrene at 10 ppm. Desorption efficiency studies [255] were conducted with amounts of styrene that would be collected from 10-liter air samples containing styrene at 50, 100, and 200 ppm. The desorption efficiencies were 0.87, 0.88, and 0.93, respectively. This method [259] is capable of measuring amounts of styrene smaller than the amounts used to evaluate it, if the desorption efficiency is determined to be adequate. The desorption efficiency must be determined over the range of concentrations to be sampled.

The method has been evaluated for precision and accuracy with styrene over the range of 100-400 ppm at 0% relative humidity and at an atmospheric temperature of 23°C and a pressure of 754 mm Hg [255]. This evaluation was performed using 5-liter air samples collected at 200 ml/min. The coefficient of variation for the total analytical and sampling method was 0.057. On the average the combined sampling and analytical method underestimated the nominal concentrations by about 8%. The method has not been tested with styrene for precision and accuracy by NIOSH below 100 ppm. However, field data from NIOSH indicates that the method has acceptable precision below 5 ppm [342].

(b) The upper limit of the range of the method is dependent on the adsorptive capacity of the charcoal tube. This capacity varies with the concentrations of styrene and other substances in the air. It was estimated that 36 mg of styrene was the maximum amount that could be collected on 100 mg of charcoal in the front (adsorbing) section before the styrene penetrated in significant amounts (i.e., 5%) to the reserve section [255]. This estimate was based on a sampling rate of 0.19 liters/min for 111 minutes in a test atmosphere that contained 400 ppm of styrene.

Interferences

(a) The volume at which breakthrough occurs in a charcoal tube is severely reduced when the humidity is high, at which time a smaller air sample should be taken or a larger charcoal tube should be used.

(b) When other compounds are known or suspected to be present in the air, the suspected identities of those compounds should be recorded.

(c) Any compound that has the same retention time as styrene using the chromatographic conditions described in this method will interfere with analysis. Such interferences may be eliminated by altering the operating conditions of the gas chromatograph or by changing the column liquid phase.

(d) Retention time data obtained by gas chromatography on a single column cannot be considered proof of chemical identity.

Apparatus

(a) Gas chromatograph (GC) equipped with a flame ionization detector.

(b) Stainless steel column (10 feet long x 1/8 inch outer diameter) with 10% free fatty acid polymer (FFAP) stationary phase on 80/100 mesh Chromosorb W HP (or equivalent), acid washed and treated with dimethyldichlorosilane (DMCS).

(c) Recorder and some method for determining peak area.

(d) Glass stoppered microtubes or vials, which can be sealed with Teflon-lined caps, that have a capacity twice the volume of carbon disulfide used for desorption (1 ml for standard size tubes).

(e) Microsyringes of appropriate size for preparing standards.

(f) Pipets that can accurately deliver the volume of carbon disulfide needed for the charcoal tubes used, such as 1.0 ml graduated in 0.1 ml increments.

(g) Volumetric flasks of appropriate sizes for preparing standard solutions.

Reagents

(a) Carbon disulfide, chromatographic quality.

(b) Styrene, reagent grade.

(c) Nitrogen, purified.

(d) Hydrogen, prepurified.

(e) Air, filtered, compressed.

Analysis of Samples

(a) Sample Preparation

Wash the equipment used for analysis in detergent followed by a tap water rinse and finally a distilled (not deionized) water rinse.

Score the charcoal tube with a file in front of the first (adsorbing) section of charcoal and break it open. Remove the glass wool and discard it. Transfer the charcoal from the first section to a 2-ml stoppered test tube or container. Remove and discard the separating foam and transfer the charcoal from the second (backup) section to another, similar, test tube or container. The two sections of charcoal are analyzed separately. Prior to analysis, when charcoal tubes containing 100 mg of charcoal in the adsorbing section are used, pipet (not by mouth) 1.0 ml of carbon disulfide into each sample container to desorb styrene from the charcoal. Use this same ratio of carbon disulfide to charcoal if larger charcoal tubes are used. A desorption time of at least 30 minutes, with occasional agitation, is recommended. It is further recommended that samples be analyzed as soon as possible after desorption; this will help prevent losses due to sample decomposition.

EXTREME CAUTION MUST BE EXERCISED AT ALL TIMES WHEN USING CARBON DISULFIDE BECAUSE OF ITS HIGH TOXICITY AND FIRE AND EXPLOSION HAZARDS. IT CAN BE IGNITED BY HOT STEAM PIPES. ALL WORK WITH CARBON DISULFIDE SHOULD BE PERFORMED UNDER AN EXHAUST HOOD.

(b) GC conditions (should be optimized according to the manufacturer's specifications). Typical operating conditions for the gas chromatograph are:

(1) 50 ml/min (60 psig) nitrogen carrier gas flow.

(2) 65 ml/min (24 psig) hydrogen gas flow to detector.

(3) 500 ml/min (50 psig) air flow to detector.

(4) 195°C injector temperature.

(5) 255°C manifold temperature (detector).

(6) 109°C column temperature.

(c) Injection of sample

To eliminate difficulties that may arise from blowback or distillation within the syringe needle, the solvent flush injection technique should be used for injection of the sample into the gas chromatograph. With this technique, the syringe is first flushed with carbon disulfide several times to wet the barrel and plunger and then 3 µl of carbon disulfide is drawn

into the syringe to increase the accuracy and reproducibility of the injected sample volume. The syringe needle is removed from the carbon disulfide and the plunger is pulled back about 0.2 µl so that the solvent flush is separated from the sample with a pocket of air, which may be used as a marker. The needle is then immersed in the sample, and a 5-µl portion is withdrawn. The volume of the needle is taken into consideration since the sample in the needle will be completely injected. After the needle is removed from the sample, and prior to injection, the plunger is pulled back a short distance to minimize evaporation of the sample from the tip of the needle. It is recommended that duplicate injections of each sample and standard be made. Using this technique, the maximum difference expected between results of duplicate injections is 3%.

Other injection techniques, such as use of automatic sample injectors, are acceptable if their reproducibility is at least as good as the solvent flush injection technique.

(d) Measurement of area

Measure the area of the sample peak by an electronic integrator or some other suitable form of area measurement, and read the preliminary results from a standard curve prepared as discussed below.

Determination of Desorption Efficiency

It is necessary to determine the percentage of styrene on the charcoal that is removed by the desorption process. This desorption efficiency may vary with the amount of styrene adsorbed onto the charcoal and the adsorption characteristics of the batch of charcoal being used. These variables necessitate determination of a desorption efficiency curve for each batch of charcoal as described below for 100-mg quantities of charcoal. Charcoal from the batch used in preparing the sample tubes can be obtained from unused tubes of the same batch.

Measure 100-mg quantities of charcoal into glass tubes that are 5 cm long, 4 mm inside diameter, and flame-sealed at one end. Inject known amounts of styrene directly into the charcoal with a microliter syringe, and cap the tubes with an inert plastic (e.g., Parafilm).

At least five tubes that contain different amounts of styrene are prepared in this manner and allowed to stand at least overnight to ensure complete adsorption of styrene onto the charcoal. Preparation of replicate tubes with each amount of added styrene is recommended. These tubes will be referred to as the desorption samples. Prepare a parallel blank tube in the same manner, except for addition of styrene. Desorb and analyze the desorption samples and blanks in exactly the same manner as previously described.

Prepare desorption standards by injecting the same volumes of styrene into 1.0 ml of carbon disulfide with the same syringe used in the preparation of the desorption samples. Replicate standards are recommended with each amount of added styrene. These are analyzed with the desorption samples.

The desorption efficiency equals the difference between the average GC peak area due to styrene recovered from the charcoal and the corresponding peak area due to the charcoal blank divided by the average peak area due to styrene added directly to the carbon disulfide or,

$$\text{desorption efficiency} = \frac{\text{area of desorption sample - area of blank}}{\text{area of standard}}$$

The desorption efficiency is plotted vs. weight of styrene found, and the curve is used for correction for incomplete desorption.

Calibration and Standards

It is convenient to prepare standards in terms of milligrams of styrene/1.0 ml of carbon disulfide if samples are desorbed in this amount of carbon disulfide. To minimize error due to variability of carbon disulfide, 10 times the weight of styrene can be injected into 10 ml of carbon disulfide. For example, to prepare 0.2 mg/1.0 ml of standard, inject 2.0 mg of styrene into exactly 10 ml of carbon disulfide in a glass-stoppered flask. Use the density of styrene (0.9018 g/cu cm at 25°C) to convert mg into µl for easy measurement with a microliter syringe.

Prepare a series of standards, varying the amount of added styrene over the range of interest, and analyze them under the same GC conditions and during the same time period as the unknown samples. Establish curves by plotting average peak area vs. milligrams of styrene/volume of carbon disulfide used for desorption.

Alternatively, carbon disulfide containing a predetermined amount of an internal standard can be used, and the styrene concentration in mg/ml can be plotted against the ratio of the area of styrene to the area of the internal standard. However, it needs to be established whether the concentration of the internal standard in solution is changed by adsorption on the charcoal.

Calculations

(a) From the standard curve, read the weight in milligrams that corresponds to the peak area. No volume corrections are needed since the standard curve is based on mg styrene/volume of carbon disulfide used for desorption, and the volume of sample injected is identical to the volume of the standards injected.

(b) The weights of styrene on the front and reserve sections of the charcoal tube must be determined separately.

(c) Corrections to the styrene weights, determined on both the front and reserve sections, for the weights of the respective sections of the blank charcoal tube are made in the following manner:

(1) Subtract the weight of styrene found on the front (adsorbing) section of the blank charcoal tube from the weight of styrene found on the front section of the sample charcoal tube to determine the corrected front section weight.

(2) Subtract the weight of styrene found on the reserve (backup) section of the blank charcoal tube from the weight of styrene found on the reserve section of the sample charcoal tube to determine the corrected reserve section weight.

(3) Add the corrected amounts of styrene present on the front and backup sections of the sample tube to determine the total amount of styrene in the sample, and divide this total weight by the appropriate desorption efficiency to obtain M, the total (corrected) milligrams per sample. The sample should be considered invalid if the backup section contains more than 20% of the amount of styrene on the front section.

(d) Convert the liters of air sampled (V) to the volume (V') at standard conditions of 25°C and 760 mm Hg, as follows:

$$V' = \frac{298VP}{760(T+273)} = \frac{0.392VP}{(T+273)}$$

Where:

V' = volume of sampled air in liters at 25°C and 760 mm Hg
V = measured volume of sampled air in liters
P = barometric pressure in mm Hg, measured at time of sampling
T = temperature of air in degrees Celsius, measured at time of sampling

(e) The concentration of styrene in the sampled air at the standard conditions (25°C, 760 mm Hg) can be expressed in various ways using M, the weight of styrene obtained in (c)(3), and V', the standardized sample volume, obtained in (d), as follows:

(1) mg/l = M/V'

(2) mg/cu m = µg/liter = 1,000 M/V'

(3) ppm = 235 M/V'

XI. APPENDIX II

DETERMINATION OF MANDELIC ACID IN URINE

General Considerations

About 50-85% of absorbed styrene is eliminated as urinary mandelic acid in humans [88,144,148]. Urinary mandelic acid has been demonstrated to correlate with time-weighted average (TWA) styrene exposures [79,91,92,125, 282]. Another major styrene metabolite, urinary phenylglyoxylic acid, can also be effectively determined, but this information adds little information to that gained from the determination of mandelic acid [156].

Urine contains many substances that may react with the reagents used to determine mandelic acid by colorimetric and polarographic methods. In colorimetric methods, phenols react with sulfuric acid-formalin [121], and lactic acid reacts with ferric chloride [144]; in polarographic analysis, phenylalanine, as well as mandelic acid, will be converted to benzaldehyde [144], the material that is analyzed. Because of varying interferences from such substances, these colorimetric and polarographic methods are not specific and cannot be relied upon to give accurate results at low urinary concentrations of mandelic acid. However, because of their simplicity, colorimetric and polarographic methods may be useful for spot checks when other analytical methods are not readily available.

Gas chromatography can be specific for mandelic acid in urine; methods have been well developed, interferences are minimal, and sensitivity is sufficient to evaluate occupational exposures to styrene. The method of Engstrom and Rantanen [79], as modified by Riihimaki and Pfaffli [154], has been successfully used to relate urinary concentrations of mandelic acid to the 8-hour TWA styrene exposures of workers and is presented at the end of this appendix; mandelic acid is analyzed by gas chromatography as its trimethylsilyl derivative. In 1979, Wilson et al. [343] used a similar method that included the use of phenyllactic acid as an internal standard.

Biological monitoring should consist of the collection and analysis of each worker's urine for mandelic acid at the time of personal industrial hygiene monitoring of airborne styrene. Mandelic acid concentrations in urine samples collected at the end of a workshift have been found to be roughly proportional to TWA styrene exposures. Because a substantial portion of styrene absorbed during a workshift is still present the next day [92,159,282], the measured value of urinary mandelic acid may reflect styrene exposure within the preceding 24 hours.

Based on the gas chromatographic method described below, on the average, a urinary mandelic acid concentration of 1,200 mg/l (adjusted to a specific gravity of 1.018) corresponds to an average 8-hour TWA styrene exposure estimate of 55 ppm, with 95% confidence limits of about 25-120 ppm (see

Figure V-1, p. 141). If the urine samples have a low specific gravity (i.e., below 1.010), additional samples should be collected. Correction may also be made by dividing the amount of mandelic acid by the amount of creatinine in the sample [92].

Because of the individual variability of urinary mandelic acid values relative to airborne styrene concentrations, urinary mandelic acid measurements serve only as a guide to estimate the overall worker exposure to styrene. However, if urinary mandelic acid concentrations tend to exceed 1,200 mg/l (adjusted to a specific gravity of 1.018), the work setting should be evaluated to identify the source of exposure. Among the possible sources that may need to be reevaluated are TWA exposure concentrations, exposure to some other substances such as ethylbenzene, improper work practices resulting in significant percutaneous styrene absorption or, conceivably, styrene ingestion or nonoccupational exposure. Among nonoccupational sources that result in urinary mandelic acid elimination are hobbies that result in styrene exposures and the use of medications that may be sources of mandelic acid.

If immediate processing of collected urine samples is not possible, the samples should be kept in a refrigerator at 4°C; Flek and Sedivec [281] found that urine samples remained unchanged for at least 14 days under those conditions.

Recommended Analytical Method [79,154]

(a) Principle of the Method

(1) Urine is collected from workers at or near the end of a workshift; specific gravity is measured.

(2) The urine is acidified with HCl, saturated with sodium chloride, and extracted with diethyl ether.

(3) An appropriate volume of the extract is removed and evaporated to dryness.

(4) A pyridine-N,O-bis-(trimethylsilyl)-trifluoroacetamide (BSTFA) solution is added (to silylate the mandelic acid) and the mixture is allowed to react at room temperature for a few minutes.

(5) A portion of the reacted material is injected directly into a gas chromatograph.

(6) The amount of mandelic acid in the urine is proportional to the height of the silylated mandelic acid GC peak; peak identification is made by comparing retention time with that of authentic silylated mandelic acid.

(b) Efficiency, Reproducibility, and Range of the Method

The mean concentration found in 10 replicate samples of urine containing 1.6 mg mandelic acid (equivalent to a concentration of 800 mg/l of urine) was 750 mg/l, an average recovery of 94% [79]. The coefficient of variation determined from replicate analyses was about 2%. The peak heights of the plot from the gas chromatograph were proportional to the concentration of mandelic acid added to normal urine over the range of 0-800 mg/l.

(c) Advantages of the Method

The collection of samples and their subsequent analysis is simple and rapid. The method can detect low concentrations and small changes in the excretion of mandelic acid; blank samples indicate little or no interference from the reagents or other substances present in the sample.

(d) Apparatus

(1) Gas chromatograph (GC) equipped with a flame ionization detector.

(2) Stainless steel column (4.6 feet long x 1/8-inch outer diameter) with 10% OV-17 stationary phase on 80/100 mesh Chromosorb W HP (or equivalent).

(3) Recorder.

(4) Microsyringes and pipets of appropriate sizes for preparing standards.

(e) Reagents

(1) Diethyl ether.

(2) Hydrochloric acid, 6N

(3) Sodium chloride.

(4) Pyridine.

(5) N,O-bis-(trimethylsilyl)-trifluoroacetamide (BSTFA).

(f) Analysis of Samples

(1) Sample Preparation

All glassware is thoroughly cleaned and rinsed. A 2-ml portion of urine is pipetted into a test tube or other convenient container and is

acidified with 40 µl of 6N HCl and saturated with NaCl. The mixture is diluted to 10 ml with diethyl ether and is shaken for 10 minutes.

A 0.5- to 5.0-ml portion of the ether extract is evaporated to dryness, and a pyridine-BSTFA (1:1,v/v) mixture is added to the residue to obtain a volume of 100 µl. After a few minutes at room temperature, a portion (1-2 µl) of the reaction mixture is injected into a gas chromatograph.

(2) GC Conditions (should be optimized according to the manufacturer's specifications). Typical operating conditions for the gas chromatograph are as follows:

(A) 15 ml/min nitrogen carrier gas flow.

(B) 60 ml/min hydrogen gas flow to detector.

(C) 300 ml/min air flow to detector.

(D) 200°C injector temperature.

(E) 320°C manifold temperature (detector).

(F) 155°C oven temperature.

(g) Calibration and Standards

It is convenient to prepare standards in terms of mg of mandelic acid/liter of urine (1 mg mandelic acid/ml of urine is equivalent to 1,000 mg/l). To minimize errors in weighing and measuring, a concentrated solution can be prepared, and a series of standards can be made by pipetting varying volumes from the concentrated solution into a series of volumetric flasks. The standards are treated the same as the urine samples. Measured volumes (1-2 µl) of the standards are injected into a gas chromatograph using the same solvent flush technique recommended for styrene analysis which was discussed in Appendix I; a standard curve is prepared by plotting peak heights vs. the amounts of mandelic acid injected.

Each time the analysis is performed a blank tube and at least one standard tube (in the midrange of the analysis) should also be analyzed so that corrections for day-to-day variation in technique or reagents can be made.

(h) Calculations

(1) The weight of mandelic acid in the sample is determined by comparing the peak height of the sample with the standard curve.

(2) The volume (V) of urine represented by the sample that was injected into the gas chromatograph is determined as follows:

$$V = a \times b \times c$$

Where:

a = volume of urine treated for analysis

b = fraction of the ether extract evaporated to dryness

c = fraction of silylated mixture injected into GC

For example, if 2 ml of urine was treated for analysis (a=2), and if a 5-ml portion of the ether extract was evaporated (b=5/10), and if 1.5 µl of the reaction mixture was injected (C=1.5/100), then the volume (V) of urine injected would be 0.015 ml.

(3) The concentration (C=µg/ml=mg/l) of mandelic acid in the urine sample is determined by dividing the weight of mandelic acid in µg found in (1) by the urine volume V

(4) The concentration of mandelic acid obtained in (3) is converted to the concentration in urine at specific gravity of 1.018 as follows:

$$C' = \frac{18C}{(SG-1.000)\ 1,000}$$

Where:

C' = corrected concentration (mg/l)

C = measured concentration (mg/l)

SG = measured specific gravity of the urine sample

XII. APPENDIX III

MATERIAL SAFETY DATA SHEET

The following items of information which are applicable to a specific product or material shall be provided in the appropriate block of the Material Safety Data Sheet (MSDS).

The product designation is inserted in the block in the upper left corner of the first page to facilitate filing and retrieval. Print in upper case letters as large as possible. It should be printed to read upright with the sheet turned sideways. The product designation is that name or code designation which appears on the label, or by which the product is sold or known by workers. The relative numerical hazard ratings and key statements are those determined by the rules in Chapter V, Part B, of the NIOSH publication, A Recommended Standard....An Identification System for Occupationally Hazardous Materials [306]. The company identification may be printed in the upper right corner if desired.

(a) Section I. Production Identification

The manufacturer's name, address, and regular and emergency telephone numbers (including area code) are inserted in the appropriate blocks of Section I. The company listed should be a source of detailed backup information on the hazards of the material(s) covered by the MSDS. The listing of suppliers or wholesale distributors is discouraged. The trade name should be the product designation or common name associated with the material. The synonyms are those commonly used for the product, especially formal chemical nomenclature. Every known chemical designation or competitor's trade name need not be listed.

(b) Section II. Hazardous Ingredients

The "materials" listed in Section II shall be those substances which are part of the hazardous product covered by the MSDS and individually meet any of the criteria defining a hazardous material. Thus, one component of a multicomponent product might be listed because of its toxicity, another component because of its flammability, while a third component could be included both for its toxicity and its reactivity. Note that a MSDS for a single component product must have the name of the material repeated in this section to avoid giving the impression that there are no hazardous ingredients.

Chemical substances should be listed according to their complete name derived from a recognized system of nomenclature. Where possible, avoid using common names and general class names such as "aromatic amine," "safety solvent," or "aliphatic hydrocarbon" when the specific name is known.

The "%" may be the approximate percentage by weight or volume (indicate basis) which each hazardous ingredient of the mixture bears to the whole mixture. This may be indicated as a range or maximum amount, i.e., "10-40% vol." or "10% max. wt." to avoid disclosure of trade secrets.

Toxic hazard data shall be stated in terms of concentration, mode of exposure or test, and animal used, e.g., "100 ppm LC50-rat," "25 mg/kg LD50-skin-rabbit," "75 ppm LC man," "permissible exposure from 29 CFR 1910.1000," or, if not available, from other sources such as publications of the American Conference of Governmental Industrial Hygienists (ACGIH) or the American National Standards Institute, Inc (ANSI). Flashpoint, shock sensitivity, or similar descriptive data may be used to indicate flammability, reactivity, or similar hazardous properties of the material.

(c) Section III. Physical Data

The data in Section III should be for the total mixture and should include the boiling point and melting point in degrees Fahrenheit (Celsius in parentheses); vapor pressure, in conventional millimeters of mercury (mm Hg); vapor density of gas or vapor (air = 1); solubility in water, in parts/hundred parts of water by weight; specific gravity (water = 1); percent volatiles (indicated if by weight or volume) at 70°F (21.1°C); evaporation rate for liquids or sublimable solids, relative to butyl acetate; and appearance and odor. These data are useful for the control of toxic substances. Boiling point, vapor density, percent volatiles, vapor pressure, and evaporation are useful for designing proper ventilation equipment. This information is also useful for design and deployment of adequate fire and spill containment equipment. The appearance and odor may facilitate identification of substances stored in improperly marked containers, or when spilled.

(d) Section IV. Fire and Explosion Data

Section IV should contain complete fire and explosion data for the product, including flashpoint and autoignition temperature in degrees Fahrenheit (Celsius in parentheses); flammable limits, in percent by volume in air; suitable extinguishing media or materials; special firefighting procedures; and unusual fire and explosion hazard information. If the product presents no fire hazard, insert "NO FIRE HAZARD" on the line labeled "Extinguishing Media."

(e) Section V. Health Hazard Information

The "Health Hazard Data" should be a combined estimate of the hazard of the total product. This can be expressed as a TWA concentration, as a permissible exposure, or by some other indication of an acceptable standard. Other data are acceptable, such as lowest LD50 if multiple components are involved.

Under "Routes of Exposure," comments in each category should reflect the potential hazard from absorption by the route in question. Comments should indicate the severity of the effect and the basis for the statement if possible. The basis might be animal studies, analogy with similar products, or human experiences. Comments such as "yes" or "possible" are not helpful. Typical comments might be:

Skin Contact--single short contact, no adverse effects likely; prolonged or repeated contact, possibly mild irritation.

Eye Contact--some pain and mild transient irritation; no corneal scarring.

"Emergency and First Aid Procedures" should be written in lay language and should primarily represent first-aid treatment that could be provided by paramedical personnel or individuals trained in first aid.

Information in the "Notes to Physician" section should include any special medical information which would be of assistance to an attending physician including required or recommended preplacement and periodic medical examinations, diagnostic procedures, and medical management of overexposed workers.

(f) Section VI. Reactivity Data

The comments in Section VI relate to safe storage and handling of hazardous, unstable substances. It is particularly important to highlight instability or incompatibility to common substances or circumstances, such as water, direct sunlight, steel or copper piping, acids, alkalies, etc. "Hazardous Decomposition Products" shall include those products released under fire conditions. It must also include dangerous products produced by aging, such as peroxides in the case of some ethers. Where applicable, shelf life should also be indicated.

(g) Section VII. Spill or Leak Procedures

Detailed procedures for cleanup and disposal should be listed with emphasis on precautions to be taken to protect workers assigned to cleanup detail. Specific neutralizing chemicals or procedures should be described in detail. Disposal methods should be explicit including proper labeling of containers holding residues and ultimate disposal methods such as "sanitary landfill" or incineration." Warnings such as "comply with local, state, and Federal antipollution ordinances" are proper but not sufficient. Specific procedures shall be identified.

(h) Section VIII. Special Protection Information

Section VIII requires specific information. Statements such as "Yes," "No," or "If necessary" are not informative. Ventilation requirements should be specific as to type and preferred methods. Respirators shall be

specified as to type and NIOSH or Mine Safety and Health Administration approval class, i.e., "Supplied air," "Organic vapor canister," etc. Protective equipment must be specified as to type and materials of construction.

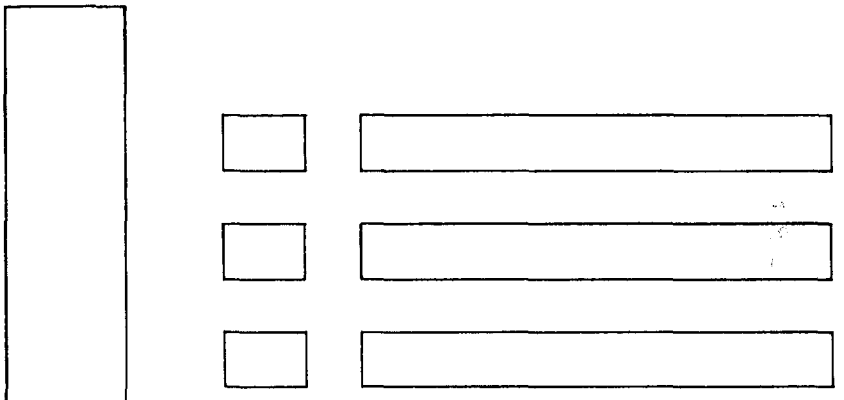
(i) Section IX. Special Precautions

"Precautionary Statements" shall consist of the label statements selected for use on the container or placard. Additional information on any aspect of safety or health not covered in other sections should be inserted in Section IX. The lower block can contain references to published guides or in-house procedures for handling and storage. Department of Transportation markings and classifications and other freight, handling, or storage requirements and environmental controls can be noted.

(j) Signature and Filing

Finally, the name and address of the responsible person who completed the MSDS and the date of completion are entered. This will facilitate correction of errors and identify a source of additional information.

The MSDS shall be filed in a location readily accessible to workers exposed to the hazardous substance. The MSDS can be used as a training aid and basis for discussion during safety meetings and training of new workers. It should assist management by directing attention to the need for specific control engineering, work practices, and protective measures to ensure safe handling and use of the material. It will aid the safety and health staff in planning a safe and healthful work environment and in suggesting appropriate emergency procedures and sources of help in the event of harmful exposure of workers.



MATERIAL SAFETY DATA SHEET

I PRODUCT IDENTIFICATION	
MANUFACTURER'S NAME	REGULAR TELEPHONE NO. EMERGENCY TELEPHONE NO.
ADDRESS	
TRADE NAME	
SYNONYMS	

II HAZARDOUS INGREDIENTS		
MATERIAL OR COMPONENT	%	HAZARD DATA

III PHYSICAL DATA		
BOILING POINT, 760 MM HG		MELTING POINT
SPECIFIC GRAVITY (H_2O=1)		VAPOR PRESSURE
VAPOR DENSITY (AIR=1)		SOLUBILITY IN H_2O % BY WT
% VOLATILES BY VOL		EVAPORATION RATE (BUTYL ACETATE=1)
APPEARANCE AND ODOR		

IV FIRE AND EXPLOSION DATA

FLASH POINT (TEST METHOD)		AUTOIGNITION TEMPERATURE	
FLAMMABLE LIMITS IN AIR, % BY VOL.	LOWER		UPPER
EXTINGUISHING MEDIA			
SPECIAL FIRE FIGHTING PROCEDURES			
UNUSUAL FIRE AND EXPLOSION HAZARD			

V HEALTH HAZARD INFORMATION

HEALTH HAZARD DATA

ROUTES OF EXPOSURE

INHALATION

SKIN CONTACT

SKIN ABSORPTION

EYE CONTACT

INGESTION

EFFECTS OF OVEREXPOSURE

ACUTE OVEREXPOSURE

CHRONIC OVEREXPOSURE

EMERGENCY AND FIRST AID PROCEDURES

EYES:

SKIN:

INHALATION:

INGESTION:

NOTES TO PHYSICIAN

VI REACTIVITY DATA

CONDITIONS CONTRIBUTING TO INSTABILITY

INCOMPATIBILITY

HAZARDOUS DECOMPOSITION PRODUCTS

CONDITIONS CONTRIBUTING TO HAZARDOUS POLYMERIZATION

VII SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

NEUTRALIZING CHEMICALS

WASTE DISPOSAL METHOD

VIII SPECIAL PROTECTION INFORMATION

VENTILATION REQUIREMENTS

SPECIFIC PERSONAL PROTECTIVE EQUIPMENT

RESPIRATORY (SPECIFY IN DETAIL)

EYE

GLOVES

OTHER CLOTHING AND EQUIPMENT

IX SPECIAL PRECAUTIONS

PRECAUTIONARY
STATEMENTS

OTHER HANDLING AND
STORAGE REQUIREMENTS

PREPARED BY

ADDRESS:

DATE:

XIII. TABLES

TABLE XIII-1

END-USES OF STYRENE

Polystyrene	Insulation board, loose-fill packaging, disposable dinnerware, food containers, toys, games, hobby kits, housings for room air conditioners and small handheld appliances, television cabinets, shower doors, drain pipes, tubing, light diffusers, audio and video tape cassettes, combs, brushes, eyeglasses, picnic coolers, molded shutters, furniture parts, watering cans, soap dishes, room dividers
Acrylonitrile-Butadiene-Styrene (ABS)	Piping (drain, waste, and vent), conduit, pipefittings, automotive components (instrument panels, consoles, front radiator grilles, headlight housings, etc.), refrigerator doorliners and food compartments, telephones, luggage and cases, toys, hobby kits, shower stalls and bathroom fixtures for mobile homes, margarine tubs, radio chassis
Styrene-Acrylonitrile (SAN)	Drinking tumblers, blender jars and covers, dishes, instrument panel lenses, battery cases
Styrene-Butadiene Latexes	Tufted carpet and upholstery backcoatings, binder for paper coatings, binder for felt base of vinyl floor tile, cement additive, component of latex paints
Other Copolymers	Ion-exchange resins (divinylbenzene-modified polystyrene), paints, paper coatings, and floor polishes (styrene-acrylic copolymer emulsions), footwear and adhesives (styrene block copolymers)
Styrene-Butadiene Rubber (SBR)	Passenger car tires, industrial hoses, conveyer belts, appliance parts, wire and cable insulation, footwear, coated fabrics, car bumpers and weatherstrips, additive in cements and adhesives
Unsaturated Polyester Resins (Reinforced plastics/composites)	Boats, open storage tanks, tub and shower units truck camper tops, recreational vehicles, wall panels

Adapted from references [23,25,344,345].

TABLE XIII-2

Occupational Styrene Exposures by Worksite or Process
(Excluding the Reinforced Plastics/Composites Industry)

Worksite or Process	Reference	Year	Samples	Styrene, ppm		Comments
				Range	Average	
Styrene Monomer Production	[56]	'52	6	ND	*	NAM
	[84]	'74	29	0.8-7.8	2.5	
	[75]	'78	60	ND-6.8	0.5	LDL:1 ppb
	[31]	'80	*	<10	*	NAM
SAN Copolymer Production	[93]	'71	*	< 1.2	<1.2	NAM
ABS-SAN Resin Production	[333]	'77	11	ND-3.1	0.7	LDL:10 ppb
Copolymer Production (maleic anhydride)	[84]	'74	6	0.9-2.1	1.5	
Styrene-Butadiene Latex Production	[84]	'74	11	1.0-3.9	2.5	
	[31]	'80	*	4-22	*	NAM
Acrylic Ester-Styrene Copolymer Production	[346]	'82	50	ND-20	0.6	LDL:10 ppb
alpha-Methyl Styrene Production	[347]	'80	14	ND-0.1	0.03	LDL:2 ppb
Polystyrene Production	[56]	'52	2	ND-188*	NAM	
	[94]	'63	*	0.05-2.2	<2.2	NAM
	[93]	'71	*	< 5	<5	NAM
	[84]	'74	13	1.2-18	7.2	
	[32]	'74	*	< 5	<5	
	[333]	'77	11	ND-1.7	0.2	LDL:100 ppb
	[75,77]	'78	70	0.1-47	1.8	
	[31]	'80	*	<10	*	NAM
SBR Production	[348]	'44	*	< 500*	NAM	
	[349]	'68	*	14-31*	NAM	
	[350]	'77	50	0.05-10	0.07	
	[333]	'77	119	ND-3.8	1.3	LDL:20 ppb
	[351]	'78	21	ND-2.3	0.4	LDL:20 ppb
	[352,353]	'81	57	ND-4.4	0.9	LDL:50 ppb
	[352,353]	'81	35	0.04-12	2.0	
	[354]	'82	159	0-65	1.7	CT & PDD
SBR Vulcanization/Curing	[355]	'69	*	0.5-9.4*	NAM	
	[356]	'77	18	0.06-0.18	0.10	

TABLE XIII-2 (CONTINUED)

Occupational Styrene Exposures by Worksite or Process
(Excluding the Reinforced Plastics/Composites Industry)

Worksite or Process	Reference	Year	Samples	Styrene, ppm		Comments
				Range	Average	
MISC. APPLICATIONS/USES						
Styrene-Polyester Resins						
Surface coatings	[357]	'60	*	200-700	*	NAM
Filter parts (molding)	[102]	'66	*	40-100	*	NAM
Furniture parts (molding)	[358]	'74	5	2-13	8	
Electrical parts (molding)	[159]	'74	2	50-200	125	
Putty (splicing)	[359]	'76	5	2-16	7	15-min. Peaks
Imitation ice cubes (molding)	[360]	'79	5	0.5-3.1	1.1	
Marble bath tubs & vanity tops	[361]	'81	2	15-19	17	
	[361]	'81	9	1.6-60	23	15-min. Peaks
	[361]	'81	1	82	82	5-min. Peaks
Styrene-Acrylic Pump Parts	[362]	'80	32	4-220	40	
Plastic Concrete Pouring (confined space)	[363]	'67	*	25-1000	*	DT & CGM
ABS Fabrication						
Injection Molding (dashboards)	[364]	'76	7	ND	<LD	LDL:20 ppb
Extrusion and Injection Molding	[365]	'78	4	ND	<LD	LDL:4 ppb
Injection Molding (visors)	[366]	'80	10	0.3-0.9	0.5	
Paper Coating	[367]	'75	9	0.7-3.1	1.6	
	[368]	'80	2	ND	<LD	LDL:1 ppm
Glues and Fillers	[369]	'77	5	ND-38	11	LDL:10 ppb
SBR Extrusion (hose)	[370]	'73	24	ND	<LD	LDL:5 ppb
Recording Tape	[371]	'81	13	<1	<1	
Polystyrene Injection Molding	[372]	'81	19	ND	<LD	LDL:2 ppb

Note: Unless specified as "Peaks," exposure levels are time-weighted averages
ND - none detected
* - not given
NAM - no analysis method given
LDL - lower detection limit in parts per billion (ppb) of styrene
DT & CGM - peak samples measured with detector tubes and a combustible gas meter
CT & PDD - charcoal tubes and passive diffusion dosimeters
Gas chromatography analysis techniques were used unless noted by NAM or DT-CGM.

TABLE XIII-3

Occupational Styrene Exposures in the
Reinforced Plastics/Composites Industry

Items Fabricated	Reference	Year	Samples	Styrene, ppm		Comments
				Range	Average	
Boats	[373]	'55	*	200-700	*	NAM
	[110]	'63	*	11-736	<209	NAM
	[35]	'72	15	17-292	*	
			*	1500	*	5-10 min. Peak
	[113]	'77	25	1-144	49	
			2	87-102	95	
			41	ND-111	44	LDL:0.1 ppm
	[112]	'77	*	< 1-217	3-44	1 hr.
			*	< 1-402	5-312	1 hr.
			*	< 1-324	3-171	1 hr.
			*	2-384	20-144	1 hr.
	[75]	'78	11	50-300	148	DT
	[374]	'81	23	6-90	39	
			21	4-179	52	
			57	1-399	142	
			19	13-382	71	
			100	2-509	143	
			94	26-745	203	
			19	11-371	133	
			37	10-161	86	
			77	30-466	179	
			70	43-214	86	
			18	64-187	126	
			97	1-226	63	
	[343]	'82	53	7-85	37	GM
			67	10-183	60	GM
			38	18-179	70	GM
			69	30-158	86	GM
			62	17-154	58	GM
			116	2-121	28	GM
			59	15-160	74	GM
Small parts	[110]	'63	*	3-75	<44	NAM
Big parts			*	4-329	<106	NAM

TABLE XIII-3 (CONTINUED)

Occupational Styrene Exposures in the
Reinforced Plastics/Composites Industry

Items Fabricated	Reference	Year	Samples	Styrene, ppm		Comments
				Range	Average	
Large parts	[109]	'67	10	6-94	*	POL
Truck parts	[375]	'72	60	0.2-70	9	
Storage Tanks	[376]	'73	71	10-210	*	
Bathroom fixtures	[377]	'73	18	7-188	49	
Tubs and Showers	[104]	'74	32	45-550	183	
Large Containers	[378]	'75	21	7-162	63	
Pipe connectors	[379]	'76	23	2-54	13	
	[380]	'76	24	ND-34	8	LDL:0.2 ppm
	[381]	'76	20	0.2-136	27	
Various items	[382]	'78	*	4-291	56	MED
Moldings, sheets	[75]	'78	9	50-70	*	Peaks, DT
Moldings, mats		'78	9	50-300	129	Peaks, DT
Molds	[383]	'78	1	12	12	
Aircraft parts	[36]	'79	43	6-293	36	
			18	39-1080	368	15-min. Peaks
Instrument cases	[384]	'79	12	9-48	22	
			20	4-200	44	
			9	10-700	*	Peaks, PI
Scrubber component	[385]	'79	24	ND	<LDL	LDL:0.2 ppm
Pump parts	[362]	'80	32	4-200	40	

TABLE XIII-3 (CONTINUED)

Occupational Styrene Exposures in the
Reinforced Plastics/Composites Industry

Items Fabricated	Reference	Year	Samples	Styrene, ppm		Comments
				Range	Average	
Storage tanks, pumps	[386]	'80	9	15-47	30	
Large pipes	[387]	'81	38	1-29	8	
Storage tanks, hoods, ducts	[388]	'81	12	4-35	13	
Model trucks	[389]	'81	3	ND-3	2	LDL:0.2 ppm

Note: Unless specified as "Peaks," exposure levels are time-weighted averages
* - not given
ND - none detected
NAM - analytical method not given, otherwise gas chromatographic methods were used
LDL - lower detection limit
DT - detector tubes
POL - polarography used
PI - photoioniser used
GM - geometric mean instead of average
MED - median value instead of average

TABLE XIII-4

Other Substances Found at Worksites Processing, Handling, or Using Styrene or Styrene-Containing Materials

Worksite or Process	Substances Found in Measurable Quantitites in Air Samples
Styrene Monomer Production	Benzene, ethylbenzene [31,33,56,84]; toluene [33,84]; ethane, ethylene[33]
Polystyrene Production	Ethylbenzene [32]; benzene, toluene, tricalcium phosphate dust, cadmium sulfide dust, pentane [84]; phenylether, diphenylether [32]
SBR Production	Butadiene [333,349,350,351,353,354]; toluene [350,353,354]; 4-vinyl-1-cyclohexene [350,353]; benzene [350,354]; cyclooctadiene [350]; benzene [333]; 4-isopropyl-1-methyl-cyclohexane, methanes, ethylbenzene, dust [353]
SBR Vulcanization/Curing	Toluene, 4-vinyl-1-cyclohexene, ethylbenzene, 1,5-cyclooctadiene,1,5,9-cyclododecatrienes [356]; butadiene, oil aerosols, formaldehyde, methanol, sulfur dioxide, acrolein, aromatic amines, acrylonitrile, carbon monoxide [355]
Styrene-maleic Anhydride Resin Production	Toluene [84]
Styrene-butadiene Latex Production	Toluene, benzene [84]; ammonia, formaldehyde [31,84]; butadiene, acrylic acid, hydroxyethyl acrylate, sodium pentachlorophenate, silica [31]
SAN Production	Acrylonitrile [93]
ABS Production	Acrylonitrile [333]
Acrylic Ester-Styrene Copolymer Production	Alpha-methyl styrene, methyl methacrylate, ethyl acrylate, n-butyl acrylate, 2-ethylhexyl acrylate [346]

TABLE XIII-4 (CONTINUED)

Other Substances Found at Worksites Processing, Handling, or Using Styrene or Styrene-Containing Materials

Worksite or Process	Substances Found in Measurable Quantitites in Air Samples
Miscellaneous Plastic Operations/Uses	
SBR extrusion (weatherstrips)	N-butyl acetate, asbestos, acetone, isopropyl acetate, petroleum naphtha, methyl ethyl ketone, carbon monoxide [390]
Styrene-polyester Usage	
molding (furniture parts)	Methylene chloride, petroleum naphtha [358]
molding(ice cubes)	Methyl ethyl ketone peroxide [360]
molding (marble bath tubs)	Acetone, toluene, methyl ethyl ketone, dust [361]
coating (paper)	Petroleum naphtha, toluene, xylene [367]
Styrene-acrylics Molding	Xylene, 1,1,1-trichloroethane [362]
ABS Usage	
injection molding (visors)	Butadiene, methyl ethyl ketone [366]
extrusion & injection molding	Carbon monoxide, hydrogen cyanide, butadiene, benzene, acrolein, dust, acetaldehyde, formaldehyde, aliphatic amines [365]
molding (aircraft parts)	Methylene chloride, methyl ethyl ketone, methanol, dust [36]
injection molding	Butyl-p-cresol, dust, carbon monoxide, formaldehyde [364]
Paper Coating	Formaldehyde [368]
Recording Tape	Methyl-iso-butyl ketone, toluene, 1,1,1-trichloroethane [371]
Combustion Products of Polystyrene (experiment)	Benzaldehyde, styrene oxide, acetophenone, 1-phenylethanol, phenol, formaldehyde, carbon monoxide, allylbenzene, benzene, toluene, ethylbenzene, isopropylbenzene, alpha-methyl styrene, acrylaldehyde [391]

TABLE XIII-4 (CONTINUED)

Other Substances Found at Worksites Processing, Handling, or Using Styrene or Styrene-Containing Materials

Worksite or Process	Substances Found in Measurable Quantitites in Air Samples
Reinforced Plastics/Composites	Acetone [36,113,375,376,377,378,383, 384,388]; methylene chloride [113,375,376,383,386,388]; dust [361,375,383,386,387]; fibrous glass [377,378,386,388]; toluene [113,375,376,389]; methyl ethyl ketone [113,375,383,386]; methyl-iso-butyl ketone [375,389]; silica [379,380]; MDI [104,376]; xylene [113,375]; amines [104]; naphtha, mold release agents [113];methyl acetate [113]; isopropyl alcohol, n-butyl acetate, cellosolve acetate [375]; TDI [377]; benzene, ethylbenzene [380]; benzoyl peroxide [387]; bisphenol A, diglycidyl ether of bisphenol A [389]; aliphatic hydrocarbons, perchloroethylene [383]; trichloroethylene [36]; methyl ethyl ketone peroxide [384]; styrene oxide [233,269].

TABLE XIII-5

Identification of Major Industries Producing, Using, or Handling Styrene

Industry (Use or Product)	SIC Major Group Code*
Construction (painting, concrete finishing)	15,16,17
Textiles (coated fabrics)	22
Wood Products and Furniture (RP/C - mobile home components)	24,25
Paper Products (paper coatings)	26
Chemicals and Allied Products (monomer, resins, paints, adhesives, etc.)	28
Rubber and Plastic Products (tires, molded and extruded items, RP/C - tanks, bathtubs, shower stalls, etc.)	30
Stone, Clay, Glass, and Concrete Products (pressed glass, pipe connectors, marble items)	32
Fabricated Metal Parts (painting)	34
Machinery(painting, molded parts, RP/C - TV cabinets, farm equipment, ventilation ducts, etc.)	35,36
Transportation Equipment (RP/C - boats, ships, parts)	37
Measuring Instruments; Medical Goods (surgical instruments, RP/C - instrument cases)	38
Miscellaneous Manufacturing (sporting goods, costume jewelry, buttons, signs, RP/C - swimming pools)	39
Automotive Repair Shops (RP/C)	75

*Taken from the Standard Industrial Classification Manual 1972 (U.S. GPO Stock No.041-001-00066-6).

REFERENCE INDEX

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